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Medical Miracles

Nano-engineering of new drug-releasing polymer structures is changing medical design. Bioabsorbable devices will be the next big thing.

Doug Smock -- Design News, August 15, 2005

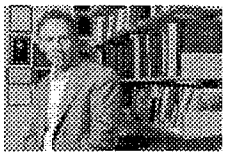
Ten years ago, design engineers didn't dare consider use of polymers for implantable medical devices. In the wake of lawsuits over use of silicones for breast implants, major polymer producers disdained offering any products for implantable applications, citing the risk of liability compared to the relatively small revenue potential.

The Situation Has Changed

Use of drug-bearing polymers in implantable devices now is exploding. From a base of zero 25 years ago, it's a $28 billion industry in the U.S. alone this year, with applications ranging from treatment of brain cancer to a potential game-changer for diabetes. The sensational success of the drug-eluting stents in particular is triggering an explosion of development in new polymers that would disappear into the body through bioabsorbtion after their use as medical devices.

Drug-eluting stents mushroomed into a $5 billion market this year from zero three years ago. Two major companies are receiving attention on Wall Street, while Medtronic and others are waiting in the wings. At the heart of the stent technology are biocompatible plastic coatings that can be timed biologically to release chemicals, even very large molecule proteins, over time.

Under development is an implantable microchip that will release scores of different drug combinations over a period of weeks or even months. Drug release can be triggered by a wireless electronic signal or through a programmed biological system.



"Design plastics from scratch that provide exactly what's needed," says Robert Langer, MIT Professor

Another possibility, farther-out, is the construction of implantable systems that can create polymer scaffolds and cell engines to replace body parts.

Shift in Device Design

The new polymer technologies signal a shift in medical device design engineering.

At its heart is MIT scientist Robert Langer, who received the coveted Stark Draper Prize in 2002 and, earlier, the Lemelson-MIT Prize. In a break from the traditional design engineering approach, Langer did not work with commercially available plastics. He instead designed his own polymers based on specific requirements. With synthetics, Langer can capture benefits of natural materials and tailor desired mechanical properties and program polymer degradation based on reaction with water.

Speaking to the recent annual technical conference of the Society of Plastics Engineers, Langer asked, "How do materials find their way into medicine? Do they find their way because of people like us who do a lot of work in plastics? It turns out that they don't. Generally the driving force has been medical doctors, who had an urgent need."

Doctors at the National Institute of Health working on an artificial heart in 1967 sought a very flexible material and suggested polyether urethanes used in ladies girdles. "It's 38 years later and guess what the artificial heart is still made of?" says Langer. Similarly, Dacron polyester fiber used in sausage casings was the original material used in vascular grafts.

"I began to think that instead of taking materials off the shelf, what if we decided, as a strategy, to design from scratch

exactly what we wanted from an engineering, biological, and chemical standpoint," Langer said.

Polymer	Initial Use	Medical Use
Polyether Urethane	Ladies Girdles	Artificial Heart
Cellulose Acetate	Sausage Casing	Dialysis Tubing
Dacron	Clothing	Vascular Graft
Silicone	Lubricant	Breast Implants
Polyurethane	Mattress Stuffing	Short-Term Implants

One of the goals was to develop polymers that eroded gradually rather than all at the same time, thereby slowing the release of toxic drugs into the body. "Then we thought do we want enzymes or water to degrade the polymer? Our thinking was we didn't want enzymes because everyone has different enzyme levels. So we picked water. We also picked chemical bonds that would be water-labile." Langer and his team then met with toxicologists and picked monomers that would be safe in the human body. They chose a polymerized type of anhydride crossed with sebacic acid. Langer discovered that the rate of release could be changed through varying the amounts of sebacic acid used in the compound. "So you can simply dial in the monomer ratio and make these last whatever length of time you want." Architecture of the polymer also affects drug release rate. Tortuous internal channels slow drug release.

The drug-releasing polymers found a variety of medical device applications, but really payed off for the treatment of coronary disease.

Reopening Arteries

Angioplasty was introduced as an alternative treatment to coronary bypass surgery around 1980 (see timeline). The approach, however, was plagued by a condition called restenosis in which muscles in the artery respond to the mechanical treatment by thickening, thereby re-closing and restricting blood flow. More than half of treatments failed as a result. Introduction of bare-metal stents reduced the restenosis rates to around 25 percent.

"Our challenge was to bring that restenosis rate down into the single-digits. We and others decided to do that by developing a drug-release stent," comments James R. Tobin, president and CEO of Boston Scientific, Natick, MA. Some 80 companies globally make stents. Close to ten began development work on a polymer-coated stent five or six years ago.

Johnson & Johnson, through its Cordis unit based in Miami Lakes, FL, was first on the market with the Cypher stent using a polymer coating developed by SurModics, Eden Prairie, MN. Close behind was Boston Scientific, which quickly grabbed market leadership and saw its stock price rise substantially over 18 months. In each design, drug and polymer are mixed together and coated on a stent. After implantation, the drug is delivered right to the spot it is needed—the great advantage of the internal drug-releasing system. It's especially important when highly toxic drugs developed to defeat cancer are used. Such drugs taken systemically could have a very negative effect on patient health.

Each company in the race uses a different polymer and drug platform. The Boston Scientific Taxus stent is an example.

Taxus uses antiinflammatory drug paclitaxel, associated with chemotherapy, to treat restenosis. "It's easier to find a drug that works than it is to find a polymer that works," comments Tobin, "Finding the right polymer carrier is difficult because it must be stable, compatible with the drug, non-inflammatory, sterilizable, expandable, and able to withstand the rigors or

handling and deployment without cracking, flaking, or delaminating."

Boston Scientific's polymer engineers spent a year studying several candidate materials before even considering what drug to use. "We had kissed every frog out there in the polymer area to try and find one that worked," Tobin responded to a question at the SPE conference. "We were struggling."

It turned out that Boston Scientific already owned a rubber-like material invented in the 1970s by Joseph Kennedy at the University of Akron, who told *Design News* that he had originally developed the material as a thermoplastic elastomer. The material is a copolymer of styrene and polyisobutylene, called SIBS, which features modifiable triblock morphology. The polymer can be designed to release the drug over different time spans. SIBS consists of soft blocks of thermoplastic elastomer and hard blocks of polystyrene. How the materials separate (as spherical, lamellar or cylindrical structures) can be programmed by varying relative weights of the two materials. The Taxus stent uses a slow release system of 30 days. Visible pores develop as the drug is released, similar to the experience in Langer's MIT lab. Taxus reduced restenois rates to 5.5 percent, according to Boston Scientific. Additionally, the butyl rubber component allows the material to expand threefold after insertion into a coronary artery.

"We have now delivered more than one million Taxus stent systems at an average selling price of about $2,500 a pop. The SIBS polymer was one of the—if not the—most critical elements that brought it all together," says Tobin.

Now there is a race on for new polymer systems to deal with another issue: the stent left behind in the body still contains some amount of powerful drug.

In Search of The Holy Grail

"The Holy Grail is a completely bioabsorbable polymer stent but it's not anywhere on the horizon for the next few years," comments Sonya Summerour Clemmons, director of business development at MediVas, LLC, San Diego, CA. For now, the push is on to commercialize a bioabsorbable coating that will release the entire drug treating restenosis.

There has already been considerable work on use of biodegradable polyesters for drug delivery inside a human body. However, these polymers do not allow very controllable timed release—the major outcome of Langer's early work. They degrade through bulk erosion. The polyesters studied could also cause an inflammatory reaction. MediVas has developed amino acid-based polyester amid copolymers that can be matrixed and conjugated in ways that allow specific release profiles from medical devices or from particles. Boston Scientific and Guidant (soon to become part of J&J) have licensed use the MediVas technologies for possible use in next-generation stents. The amount of polymer on a device is in the micrograms, Clemmons told *Design News*. A Rutgers University research team has developed a polymerization approach in which polymer carriers function as barriers and then degrade into products that influence the inflammatory process locally. New polymers may be able to address deep bone infections and various inflammatory diseases as well as restenosis. Several of the latest developments were described at the recent annual meeting of the American Chemical Society.

Meanwhile, Langer's lab at MIT is exploring other polymeric approaches that will revolutionize medical design in other ways. "Our plan is to design three-dimensional polymer scaffolds and then grow cells on the scaffold in vitro in a bioreactor," he says. "Let's say that someone comes in 20 to 30 years from now and they would like a new nose. You could then use computer-aided design and create any type of nose you want. You can take cells from the ear and grow the nose."

How do you avoid a difficult operation to insert a new body part, such as a nose? Langer again is using his design creativity to consider a new approach.

"We thought, could we develop a biodegradable polymer that would be like a string at room temperature and then grow into any shape you want at body temperature?" Dr. Langer and post-doctoral students began to study phase-segregated multi-

block copolymers which include a series of cross links that melt at certain temperatures. At another, higher temperature, other links would take over and control the shape determined by CAD. In effect, they're biodegradable shape memory plastics. In the newest twist under study, the initiator would not be heat—it would be light from a fiber optic cable that could be inserted using minimally invasive surgery. The technology could also be used to create self-tying sutures—or even drug-eluting stents. Langer and one of his post-doctoral students, Andreas Lendlein, created a company in Aachen, Germany called mnemoScience GmbH to commercialize the discovery.

In the Works: Pharmacy on a Chip

One of the drug-releasing breakthroughs under development is a microchip loaded with pharmaceuticals or other chemicals. Based on work in the MIT lab of Robert Langer, a company called MicroCHIPS in Bedford, MA, is developing tiny silicon or polymeric microchips containing up to thousands of micro-reservoirs, each of which can be filled with any combination of drugs, reagents, or other chemicals. Preprogrammed microprocessors, remote controls, or biosensors can be used to open micro reservoirs to achieve intricate chemical release models. "I'm a professor and one of the things that professors always think about is what's next that might have an impact," says Lnager. "I was watching a documentary about 11 years ago about how microchips are made in the computer industry and I thought to myself, 'Boy, would this be a great way to make a drug-delivery system.' Now if you spent 30 years of your life developing drug-delivery systems, it might turn out that any TV show might make you think that." Potential advantages of the microchip approach include small size and low power consumption, an absence of moving parts, and the capability to store and release multiple drugs or chemicals from a single device. The microchip shown here is activated through an electronic signal. Langer has also made polymeric chips that use biologically activated caps of varying molecular weights to release the drugs. It's conceivable that the device could be used in conjunction wtih an implantable insulin pump. Glucose sensors inside the mcirochip could send a message to an insulin pump implanted elsewhere in the body. Some reports have called the concept an "artificial pancreas." "In the future, what we hope to do is put little biosensors on these chips," says Langer. "Then, by using a microprocessor and a power source, we could make a smart system."

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For more information on medical polymers:

MIT's Langer Lab

TAXUS stent

CYPHER stent

Drug-eluting stent center

Shape memory plastics

Pharmacy on a chip

Surface modification of medical devices

Biodegradable medical polymers

The Battle of the Stents Timeline

The Battle of the Stents Timeline

1960s to 1994: Coronary artery bypass is the usual treatment for coronary artery blockage.

1974: Dr. Robert Langer of MIT begins studying polymers and polymeric structures that can deliver internally large molecule drugs slowly and safely (later called drug-eluting).

1980: Angioplasty is introduced.

1995-1996: Johnson & Johnson, working with Cordis, gets FDA approval for bare-metal stents, used to prop open clogged arteries.

April 2003: The Cordis unit of Johnson & Johnson launches the Cypher sirolinius-eluting stent, which is priced about three times higher than bare-metal stents. Overall Cordis sales jump 65 percent as the new device revolutionizes treatment of blocked arteries.

March 2004: Boston Scientific launches the Taxus Express drug-eluting stent, which reaches $2.1 billion in sales in 2004 and grabs 70 percent of the market.

June 2005: A J&J v. Boston Scientific patent trial—simmering for five years—opens in Wilmington, DE. J&J claims the stent infringes on its core stent patent. A counter suit by Boston Scientific is scheduled for October 2005.

The Future: Several companies explore use of moldable biodegradable polymers that would replace the metal structure.

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Clinical Investigation and Reports

Lack of Neointimal Proliferation After Implantation of Sirolimus-Coated Stents in Human Coronary Arteries

A Quantitative Coronary Angiography and Three-Dimensional Intravascular Ultrasound Study

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Background—Restenosis remains an important limitation of interventional cardiology. Therefore, we aimed to determine the safety and efficacy of sirolimus (a cell-cycle inhibitor)-coated BX Velocity stents.

Methods and Results—Thirty patients with angina pectoris were electively treated with 2 different formulations of sirolimus-coated stents (slow release [SR], n=15, and fast release [FR], n=15). All stents were successfully delivered, and patients were discharged without clinical complications. Independent core laboratories analyzed angiographic and 3D volumetric intravascular ultrasound data (immediately after procedure and at 4-month follow-up). Eight-month clinical follow-up was obtained for all patients. There was minimal neointimal hyperplasia in both groups (11.0±3.0% in the SR group and 10.4±3.0% in the FR group, P=NS) by ultrasound and quantitative coronary angiography (in-stent late loss, 0.09±0.3 mm [SR] and −0.02±0.3 mm [FR]; in-lesion late loss, 0.16±0.3 mm [SR] and −0.1±0.3 mm [FR]). No in-stent or edge restenosis (diameter stenosis ≥50%) was observed. No major clinical events (stent thrombosis, repeat revascularization, myocardial infarction, or death) had occurred by 8 months.

Conclusions—The implantation of sirolimus-coated BX Velocity stents is feasible and safe and elicits minimal neointimal proliferation. Additional placebo-controlled trials are required to confirm these promising results. (***Circulation.*** **2001; 103:192-195.)**

Key Words: stents ■ restenosis ■ angioplasty

Restenosis remains a vexing problem of percutaneous intervention. The most promising approach to prevent restenosis has been the application of intracoronary radiation[1]; however, some relevant side effects (edge restenosis and late thrombosis) have been reported.[2,3] Numerous pharmacological approaches to reduce restenosis have failed, possibly due to insufficient local drug concentrations.[4] Delivering medication directly to the site of vascular injury via polymeric-coated stents is a rational approach to achieve adequate local drug delivery.[5,6]

Sirolimus (Rapamune), a natural macrocyclic lactone, is a potent immunosuppressive agent that was developed by Wyeth-Ayerst Laboratories and approved by the Food and Drug Administration for the prophylaxis of renal transplant rejection in 1999.[7] Sirolimus binds to an intracellular receptor protein and elevates p27 levels, which leads to the inhibition of cyclin/cyclin-dependent kinase complexes and, ultimately, induces cell-cycle arrest in the late G1 phase. It inhibits the proliferation of both rat and human smooth muscle cells in vitro[8,9] and reduces intimal thickening in models of vascular injury.[10–12] However, the effects of the local administration of sirolimus in a coated stent in humans have not been reported.

The aims of this pilot study were to assess (1) the feasibility and safety of implanting 2 different formulations of the sirolimus-coated BX Velocity stent in atherosclerotic human coronary arteries and (2) the impact of the stents on neointimal proliferation.

Methods

From December 1999 to February 2000, a single sirolimus-coated BX Velocity stent was successfully implanted in each of 30 consecutive patients with coronary artery disease. The stent is a

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laser-cut, 316L stainless steel, balloon-expandable stent that contains a fixed amount of sirolimus per unit of metal surface area (140 μg of sirolimus per cm²).

Sirolimus was blended in a mixture of nonerodable polymers that have been used clinically in bone cements, ocular devices, and a drug-releasing intrauterine device.[13,14] Fifteen patients received a fast release (FR) formulation (<15-day drug release), and 15 received a slow release (SR) formulation (≥28-day drug release).

Procedure

All stents were 18 mm long and 3.0 to 3.5 mm in diameter. After predilatation of the target lesion, stents were deployed with high-pressure (>14 atm) postdilatation guided by intravascular ultrasound (IVUS). All patients received aspirin (325 mg/d, indefinitely), which was started at least 12 hours before the procedure, and clopidogrel (300 mg immediately after stent implantation and 75 mg/d for 60 days). The protocol was approved by the Medical Ethics Committee of the Institute Dante Pazzanese of Cardiology, and informed consent was obtained from every patient.

Quantitative Measurements

Quantitative coronary angiography (QCA) and IVUS imaging were performed immediately after the procedure and at 4-month follow-up in all patients after a bolus infusion of intracoronary nitrates. IVUS images were acquired using motorized pull-back at a constant speed of 0.5 mm/s. Quantitative angiographic and volumetric IVUS analyses were performed by independent core laboratories (Brigham and Women's Hospital, Boston, Mass, and Cardialysis BV, Rotterdam, The Netherlands, respectively).[15–17] Three segments were selected for volumetric IVUS analysis: the stented segment (18 mm long) and 2 edge segments that were axially 5 mm proximal and distal to the stent margins.

Statistical Analysis

Continuous variables are expressed as mean±SD. Comparisons between postintervention and follow-up measurements were performed with a 2-tailed paired *t* test. Comparisons between groups were performed using an unpaired Student's *t* test. $P<0.05$ was considered statistically significant.

Results

Twenty-six patients had stable angina and 4 patients had unstable angina. Their mean age was 57.9±10 years (SR) and 55.1±7 years (FR); 63% of the patients in each group were male. The incidence of prior myocardial infarction was 33.3% (SR) and 53.3% (FR), and 14% (FR) and 26% (SR) of the patients were diabetics. All stents were implanted successfully, and all patients were discharged without complications 24 hours after treatment. Creatine kinase and creatine kinase-MB levels, sampled at 6 and 18 hours after the procedure, were within the normal range in all patients.

Angiographic and volumetric IVUS data are presented in Tables 1 and 2. No patient approached ≥50% vessel narrowing by QCA or IVUS, and only 3 patients had >15% intimal hyperplasia (IH) by IVUS (Figure 1). In both the edge segments and in the stented segment, lumen loss detected by IVUS was minimal (Figure 2). All patients completed 4 months of angiographic and 8 months of clinical follow-up. There were no repeat revascularizations, stent thromboses, or major clinical events (cerebrovascular accident, myocardial infarction, or death).

Discussion

This is the first human experience with the implantation of sirolimus-coated BX Velocity stents. The absence of adverse events for up to 8 months of follow-up suggests that the implantation of this stent, which is coated with a potent cell-cycle inhibitor, is feasible and safe.

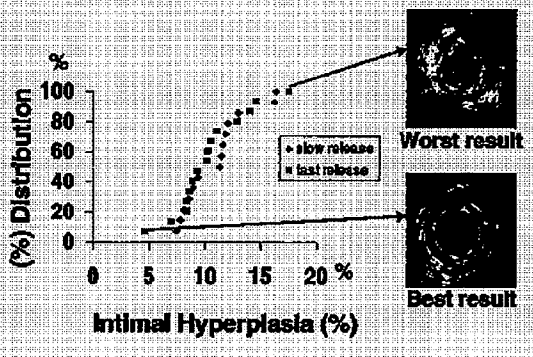

Figure 1. Left, Cumulative distribution curves of percent IH in SR and FR groups. Upper right panel shows follow-up IVUS cross-section with largest amount of IH (17.5%), and lower right panel displays IVUS cross-section with lowest amount of IH (4.6%). In both vessels, a FR stent was implanted (arrows).

The amount of IH after the implantation of noncoated stents ranges from 19% to 48% of stent volume[3,18,19] by IVUS, and late loss averages 0.3 to 0.9 mm by QCA.[19] Even in nonrestenotic stents that are ≤15 mm long, an average IH

TABLE 1. Offline Quantitative Coronary Analysis by Core Laboratory

Parameters	SR Group (n=15)	FR Group (n=15)
Before procedure		
RD, mm	2.98±0.4	2.94±0.3
MLD, mm	1.16±0.3	0.93±0.4
DS, %	62±7	68±14
Lesion length, mm	12.9±1.97	13.1±2.2
Lesion type B1,* %	27	47
Lesion type B2,* %	73	33
After procedure		
RD, mm	3.1±0.4	2.96±0.3
In-lesion MLD, mm	2.74±0.4	2.68±0.3
In-stent MLD, mm	2.94±0.44	2.84±0.3
In-lesion DS, %	11.44±5.5	9.7±5.8
In-stent DS, %	5.09±6.72	4.2±7.4
Follow-up		
RD, mm	2.99±0.4	3.07±0.3
In-lesion MLD, mm	2.6±0.5	2.7±0.4
In-stent MLD, mm	2.9±0.5	2.93±0.3
In-lesion DS, %	14.5±9.1	12.7±8.2
In-stent DS, %	5.04±6.7	4.55±5.7
In-lesion late loss, mm	0.16±0.3	−0.02±0.3
In-stent late loss, mm	0.09±0.3	−0.1±0.3

Values are mean±SD. RD indicates reference diameter; MLD, minimum lumen diameter; and DS, diameter stenosis.
*According to AHA/ACC classification

TABLE 2. Postprocedure and Follow-Up 3D IVUS Measurements by Core Laboratory

	Lumen Volume, mm³			Stent Volume, mm³			Neointimal Hyperplasia	
	Post	FUP	*P*	Post	FUP	*P*	Volume, mm³	Percent
Total	141.6±35	127.8±36	<0.01	141.6±35	142.8±39	NS	15.0±5	10.7±3.0
SR group	152.2±40	137.6±40	<0.01	152.2±40	154.4±44	NS	16.8±6	11.0±3.0
FR group	131.3±31	118.7±30	<0.01	131.3±31	132.0±31	NS	13.3±4	10.4±3.0
P	NS	NS		NS	NS		0.07	NS

Data are mean±SD, unless otherwise indicated. Post indicates postprocedure; FUP, follow-up.
*SR vs. FR.

of 19.7% has been observed by IVUS.[18] Although differences in population and stent design limit scientific comparison with other reports, it is worth noting that the amount of IH detected in the present study (10.7%; essentially zero late loss by QCA) is much lower than previously reported. This is likely due to the cytostatic effect of sirolimus.[10–12,20]

Using the same IVUS methodology, the amount of in-stent IH with radioactive stent implantation varied from 7.4% (6 to 12 μCi radioactive stent) to 16.7% (0.75 to 1.5 μCi).[17] However, neither edge restenosis nor stent thrombosis, both of which have been reported after radiation,[2,3] were observed after the implantation of sirolimus-coated stents (Figure 2).

As a result of their permanent scaffolding action, stents have become an attractive platform for delivering medications locally.[5,21] Although some polymers have been associated with a marked inflammatory reaction,[22] these findings were not observed with the polymers used in the present investigation or in other clinical situations.[13,14] In the present study, similar favorable results were observed with both the FR and SR formulations of the sirolimus-coated stent. Whether one sirolimus coating matrix is superior to the other (SR versus FR) requires further investigation.

Limitations

The study comprises a registry of only 30 patients with 4 months of QCA and 3D IVUS data and 8 months of clinical data. However, considering the absence of late loss by QCA and the virtual absence of IH observed in the present study by 3D IVUS and the well-documented degree of late loss with uncoated stents, these early results are promising. Twelve-month angiographic and IVUS follow-up will be performed in all patients to assess whether this effect is sustained.

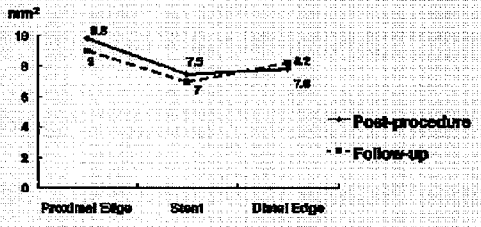

Figure 2. Postprocedure and follow-up mean lumen areas within stent and at 5-mm edge segments (n=30), as assessed by 3D IVUS.

Conclusion

Sirolimus-coated BX Velocity stents seem to be safe and effective in preventing neointimal formation at 4 months after stent implantation in de novo lesions. These seminal findings warrant further confirmation by large, placebo-controlled, multicenter trials.

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EuroIntervention

Pioneer clinical experiences: from bare metal Palmaz-Schatz™ to Sirolimus-Eluting CYPHER™ stents

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Abstract

The treatment of coronary artery disease underwent a remarkable shift over the past decades. Such progress would not be possible without the ingenuity of entrepreneurial scientists, sound clinicians and the courage of our patients. This article reports the two events that marked the beginning of modern interventional cardiology: the implantation of the first balloon-expandable stent (Palmaz-Schatz™), and the first sirolimus-eluting stent (Cypher™) in human coronary arteries. Both procedures were performed, almost a decade apart, at the Institute Dante Pazzanese of Cardiology in Sao Paulo, Brazil.

We were asked to provide a historical description of the first experiences with balloon expandable stents, i.e. bare metal and drug-eluting stents. The courage and ingenuity of pioneers such as Andreas Gruentizg, Julio Palmaz and Richard Schatz paved the way for what would soon become the preferred coronary revascularization strategy, namely intracoronary stents. In 2003, an estimated 1,244,000 PCI versus 467,000 bypass procedures were performed in the United States[1].

Our group had the privilege to implant the first balloon expandable stent (Palmaz-Schatz™; Cordis, Warren, NJ, USA) in a human coronary artery in 1987. More recently, our group was once again honored to conduct the first-in-man (FIM) experience with sirolimus-eluting stents (Cypher™, Cordis, Warren, NJ, USA). These memorable experiences will be reported in this article.

The Palmaz-Schatz™ Stent FIM experience

We were initially approached by Johnson and Johnson regarding the possibility to test a stainless steel balloon-expandable tubular fenestrated prosthesis in a human coronary artery. Dr Richard Schatz provided some preliminary data and technical explanations of what would soon be named the Palmaz-Schatz stent[2]. Despite the lack of strong regulatory agencies at the time, the ethical principles, which are an inherent part of medicine, forced us to repeat and practice the implantation procedure in the experimental laboratory at the Institute Dante Pazzanezze of Cardiology before any attempt was made to treat humans. Meanwhile, we were supposed to select the candidate for this first experiment, who needed to have a well collateralized single vessel coronary disease. As you can imagine, it was no trivial task to explain to a patient that he would undergo a procedure that had not been done in humans and that we really didn't understand the risks associated with it, while coronary artery bypass surgery was already a well establish therapeutic options for such patients. We certainly could not have predicted that stents could be associated with a 5 to 20% risk of thrombosis. Had we known better, such an experience would likely have been delayed for years or even decades, as it took almost 10 years to find the solution to the problem of stent thrombosis[3]. We did not know much about the potential benefits either. Nevertheless, we were able to identify the candidate and schedule what would represent the starting point of a new era in interventional cardiology. Luckily,

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the patient was a dental prosthesis professional, which made it easier to explain the concept of intracoronary stent – it is likely that he knew more about "stents" than us. He was 56 years old at the time, and had a history of dyslipidaemia and smoking. He had a severe stenosis in the right coronary artery and a well developed collateral from the left system. However, it took a while before we could perform the procedure, as the cine-angiograms were sent to the United States for evaluation and approval. Then, in December, 1987 after we had done 3 animal implants together with Dr Schatz, the patient returned for his procedure. Unfortunately the right coronary artery was found to be completely occluded and we had to make a decision on whether to proceed with the experiment or find another candidate. Once again thanks to our relative ignorance, we chose to proceed with the experiment without knowing that total occlusions would remain one of last hurdles of interventional cardiology, even today.

The right coronary occlusion was initially crossed with a 0.014" wire – a major technological advance at the time – through an 8F guiding catheter. Balloon pre-dilatation was performed at 6 atmospheres with a 3.0/20-mm balloon. The stent had to be hand-crimped onto the balloon prior to deployment. Deployment was performed at 8 atmospheres and post-stenting balloon dilatation was not performed. The patient was pre-treated with 300 mg of aspirin and 75 mg of dipyridamole the day prior to the procedure. At the beginning of the procedure, a continuous infusion of dextran (1000 ml) and a bolus dose of 10,000 U of heparin were administered. Post-procedure, a combination of heparin and oral anticoagulation therapy with coumadin was initiated after sheath removal. The procedure was performed in the afternoon and the patient likely had a better night of sleep than the physicians who performed his procedure, as we could not wait until the morning to bring him back to the cathlab for a re-look. Surprisingly, the vessel was open. This was back in 1987, and you can be sure that if similar circumstances and techniques occurred in 2006, the vessel would be occluded. Better to be lucky, a lesson learned from football. The patient was discharged without complications one week after the index procedure. Despite his above average educational status, the patient decided not to take his medication since he was doing so well with the procedure. Once again this patient was likely correct about his own personal "clinical" decisions because in October, 2000 he underwent angiographic and IVUS follow-up examinations (Figure 1) and had yet to suffer another cardiovascular event. There was no significant disease progression in other vessels or any restenosis detected. As you might expect, the stent was underexpanded. The in-stent minimal cross-section area (CSA) was 4.9 mm^2, while the mean proximal and distal CSA was 9.02 mm^2. The lack of intimal proliferation after the recanalization of a totally occluded vessel 13 years after deployment is puzzling as it resembles the results of the yet to be tested drug-eluting stents. The irony of his destiny was that this patient lived 14 years after the procedure without any cardiovascular complications and, sadly, died after a car accident. Why didn't he have thrombosis? Coronary disease progression? Restenosis? Other cardiovascular events? The lack of answers to these and many other questions is what makes medicine so inspiring.

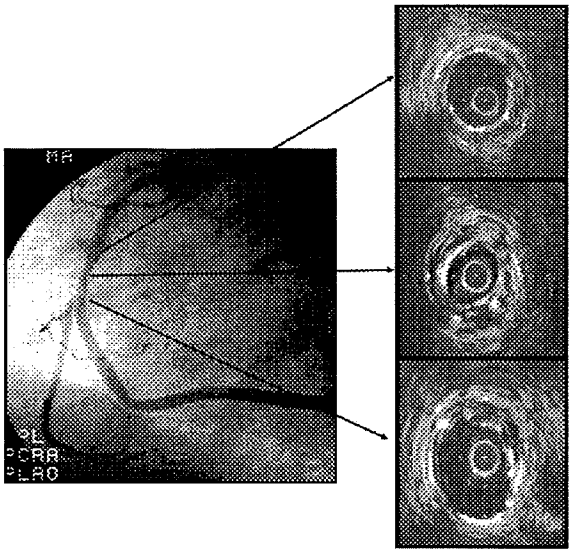

Figure 1. Angiography (right panel) and IVUS (left panels) images 13-years after the first implantation of a Palmaz-Schatz stent in a human coronary artery. IVUS revealed an under expanded coronary stent (middle panel) with almost no intimal proliferation.

The Cypher™ Stent FIM Experience

The need for a device with potent antiproliferative properties soon became apparent[4,5]. Once again we were contacted by Johnson and Johnson. Their scientists had developed and tested, in various experimental models, a stent coated with sirolimus (rapamycin). The stent was a conventional bare metal stent - laser cut 316L stainless steel balloon-expandable stent coated. The device was coated with a 5 µm thick layer of a non-biodegradable polymer blended with the drug. Rapamycin was originally developed by Wyeth-Ayerst Laboratories and had just been approved by the Food and Drug Administration (FDA) for the prophylaxis of renal transplant rejection at the time of the FIM experience in 1999. Most of the mechanisms of action of the drug were well known, and they were related to the binding of sirolimus, the FKBP complex to a specific cell cycle regulatory protein, the mTOR (mammalian target of rapamycin)[6-10]. What we did not know was the effect of such potent medication in a diseased human coronary artery. As you might remember, we were just understanding the problems associated with brachytherapy and had poor experiences with previous attempts at stent coatings.

Although we had accumulated an impressive knowledge about the mechanisms of stent deployment, mechanisms of restenosis and how energy and drugs could modulate the cell cycle to prevent proliferation, we were once again walking in the dark, with skepticism at its highest level. Unlike the Palmaz-Schatz FIM experience, which involved the treatment of a single patient, the Cypher FIM required 30 patients. The plan was to perform 15 patients on a single day, so we could appreciate the success or failure of the device at once. Initially IVUS imaging was not proposed, but our group would not miss the opportunity to look at these devices closely and all procedures were guided by IVUS as well as subsequent examinations. Two preparations of sirolimus-eluting stents were tested ini-

tially. The fast release formulation (FR) delivers the drug almost completely by 15 days after implantation, while the slow release (SR) formulation, which later became the commercially available Cypher stents, takes > 28 days for complete drug release.

The first session occurred in December, 1999 and the FR platform was selected for the 15 treatments. A month later, after the early safety of SES was confirmed, the SR SES formulations were deployed in another cohort of 15 patients, again in a single day. Yes, our group had improved our deployment techniques and stents were implanted after balloon pre-dilatation and followed by high-pressure (> 12 atmospheres) balloon post-dilatation through a 6F guiding catheter. Yet, the balloons for pre-dilatation and post-dilatation were longer than the stents, as we didn't yet appreciate the potential risks of a geographical miss at the time. Patients received aspirin (325 mg/day, indefinitely) started at least 12h before the procedure and a 300 mg loading dose of clopidogrel immediately after stent implantation. Dual antiplatelet therapy was maintained for only 2 months.

The 4-month follow-up date of the first group arrived. The Cordis team, at the time led by Judy Jaeger, arrived in Sao Paulo the day before. A mixture of disbelief and optimism increased as each angiogram was being performed. Between cases, Judy provided constant phone feedback to Bob Falotico, who had been involved with the development of this technology since the earliest days. When the angiography of patient number 15 was completed, the group was physically tired of walking up and down the stairs from cathlab room 4 and 7. Angio films and IVUS images were reviewed for each case at the end of the day and the second cohort of 15 patients returned the month following this first excitement. The scene repeated itself. At the end of the day, a group of tired physicians gathered to evaluate and celebrate what would become the first successful experience with drug-eluting stents and likely change the way we would face coronary disease for years to come[7-10]. The difference this second time was that Dr. Amanda Sousa arranged to have champagne for the celebration.

Patrick Serruys and his team were responsible for the IVUS analysis of the data. Accustomed to evaluate bare metal stents, soon after they received our follow-up IVUS tapes, they sent a request to resubmit the follow-up images because we had "wrongly sent duplicates of the index procedure". They could not believe that they were indeed looking at correct follow-up images, which were identical to the post-procedure results because the drug had abolished intimal proliferation all together. This was clarified in a meeting at the EuroPCR, when we had the opportunity to show each of the 30 cases with the index and follow-up images side by side.

Unlike the Palmaz-Schatz stent experience described above, the Cypher FIM human testing was much more regulated and closely monitored. A body of pre-clinical experience was available and yet, so little was known. It took the imagination, scientific knowledge and courage of various individuals – including the patients – to embark upon this journey. Paraphrasing Albert Einstein: *"if we knew what it was we were doing, it would not be called research, would it?"*

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Sustained Suppression of Neointimal Proliferation by Sirolimus-Eluting Stents: One-Year Angiographic and Intravascular Ultrasound Follow-Up

J. Eduardo Sousa, Marco A. Costa, Alexandre C. Abizaid, Benno J. Rensing, Andrea S. Abizaid, Luiz F. Tanajura, Ken Kozuma, Glenn Van Langenhove, Amanda G.M.R. Sousa, Robert Falotico, Judith Jaeger, Jeffrey J. Popma and Patrick W. Serruys

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Sustained Suppression of Neointimal Proliferation by Sirolimus-Eluting Stents

One-Year Angiographic and Intravascular Ultrasound Follow-Up

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Background—We have previously reported a virtual absence of neointimal hyperplasia 4 months after implantation of sirolimus-eluting stents. The aim of the present investigation was to determine whether these results are sustained over a period of 1 year.

Methods and Results—Forty-five patients with de novo coronary disease were successfully treated with the implantation of a single sirolimus-eluting Bx VELOCITY stent in São Paulo, Brazil (n=30, 15 fast release [group I, GI] and 15 slow release [GII]) and Rotterdam, The Netherlands (15 slow release, GIII). Angiographic and volumetric intravascular ultrasound (IVUS) follow-up was obtained at 4 and 12 months (GI and GII) and 6 months (GIII). In-stent minimal lumen diameter and percent diameter stenosis remained essentially unchanged in all groups (at 12 months, GI and GII; at 6 months, GIII). Follow-up in-lesion minimal lumen diameter was 2.28 mm (GIII), 2.32 mm (GI), and 2.48 mm (GII). No patient approached the ≥50% diameter stenosis at 1 year by angiography or IVUS assessment, and no edge restenosis was observed. Neointimal hyperplasia, as detected by IVUS, was virtually absent at 6 months (2±5% obstruction volume, GIII) and at 12 months (GI=2±5% and GII=2±3%).

Conclusions—This study demonstrates a sustained suppression of neointimal proliferation by sirolimus-eluting Bx VELOCITY stents 1 year after implantation. (***Circulation.* 2001;104:2007-2011.)

Key Words: angiography ■ drugs ■ stents ■ restenosis ■ ultrasonics

Despite major technological advances in the past decades, of which the coronary stent is one of the most important, the percutaneous treatment of coronary artery disease is still hampered by a 20% to 30% incidence of restenosis. The list of candidate therapies and devices for prevention of restenosis after angioplasty is long and ever expanding. However, few if any have substantially improved the result of stenting for the treatment of de novo lesions. Intracoronary radiation has so far proven to be effective for the treatment of in-stent restenosis but not for the treatment of de novo lesions.[1] As a result of their ability to deliver prolonged and sufficient intramural drug concentrations to the target coronary segment, drug-eluting stents have emerged as a potential solution for restenosis. Our group has recently reported an almost complete absence of neointimal hyperplasia 4 months after implantation of sirolimus-eluting Bx VELOCITY stents.[2] The local release of sirolimus (rapamycin, Rapamune), a natural macrocyclic lactone with potent immunosuppressive action,[3] resulted in elimination of restenosis in this first series of patients. Comparable results have only been observed after the implantation of high-activity β-emitting stents (9 mm^3 of neointimal hyperplasia at 6-month follow-up).[4] However, a worrying late progression of in-stent neointimal hyperplasia was observed between 6 months and 1 year after implantation of radioactive stents.[5]

See p 1996

The aim of the present investigation was to determine whether sirolimus-eluting stents produce a sustained suppression of the neointimal proliferation over a period of 1 year or merely delay the restenosis process.

Methods

Study Population

Forty-five patients with native coronary artery disease and angina pectoris were successfully treated with the implantation of a single

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From the Institute Dante Pazzanese of Cardiology (J.E.S., M.A.C., A.C.A., A.S.A., L.F.T., A.G.M.R.S.), São Paulo, Brazil; Thoraxcenter, Dijkzigt University Hospital (B.J.R., K.K., G.V.L. P.W.S.), Rotterdam, The Netherlands; Cordis, a Johnson and Johnson Company (R.F., J.J.), Warren, NJ; and Brigham and Women's Hospital (J.J.P.), Boston, Mass.

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sirolimus-eluting Bx VELOCITY stent. Only lesions ≤18 mm in length and vessels ≥3 and ≤3.5 mm in diameter were included. Total occlusion, ostial or thrombus containing lesions, unprotected left main disease with >50% stenosis, occurrence of myocardial infarction within the preceding 72 hours, and left ventricular ejection fraction <30% were the major exclusion criteria. Thirty patients were electively treated with two different formulations of sirolimus-eluting stents (fast release [FR], n=15, group I, and slow release [SR], n=15, group II) at the Institute Dante Pazzanese of Cardiology, São Paulo, Brazil. A third cohort of patients (n=15, group III) was treated with SR sirolimus-eluting stents at the Thoraxcenter, Erasmus University Rotterdam, The Netherlands.

Drug-Polymer Matrix and Elution Kinetics

Sirolimus was blended in a mixture of nonerodable polymers, and a 5-μm-thick layer of sirolimus-polymer matrix was applied onto the surface of the Bx VELOCITY stent (Cordis), a laser-cut 316L stainless-steel balloon-expandable stent.

The drug is almost completely eluted by 15 days after implantation in the FR formulation. Another layer of drug-free polymer was applied on top of the drug-polymer matrix to introduce a diffusion barrier and prolong drug release to >28 days in the SR formulation. All stents, regardless of the coating composition, were loaded with a fixed amount of sirolimus per unit of metal surface area (140 μg sirolimus/cm^2).

In vivo experiments have shown that sirolimus levels in whole blood peak at 1 hour (2.6±0.7 ng/mL, FR; 0.9±0.2 ng/mL, SR) after implantation and fall below the lower limit of quantification by 72 hours (0.4 ng/mL) (Bruce D. Klugherz, unpublished data, 2000). Taking into account that renal transplant patients maintain chronic blood levels of rapamycin between 8 and 17 ng/mL, the peak blood level after implantation of a sirolimus-eluting stent is absolutely negligible.

Stent Procedure

Stents were implanted according to standard practice, after balloon predilatation and followed by high-pressure (>12 atmospheres) balloon after dilatation. All stents were 18 mm long and 3 to 3.5 mm in diameter. Heparin was given to maintain the activated clotting time >300 seconds. Patients received aspirin (325 mg/d, indefinitely) started at least 12 hours before the procedure and a 300-mg loading dose of clopidogrel immediately after stent implantation and 75 mg/d for 60 days. The protocol was approved by the Medical Ethical Committees of both institutions, and written informed consent was obtained from every patient.

Angiographic and IVUS Procedures

Patients in São Paulo (groups I and II) underwent intravascular ultrasound (IVUS) and angiographic follow-up at 4 and 12 months. In Rotterdam (group III), patients returned for repeat angiography and IVUS assessment at 6 months, the classical restenosis time point. Intracoronary nitrates were administered immediately before each angiographic and IVUS acquisition. Postprocedure angiography was performed in at least 2 orthogonal projections, which were repeated at the follow-up studies. Quantitative angiographic analysis was done by an independent core laboratory (Brigham and Women's Hospital, Boston, Mass).

The segments subject to three-dimensional (3D) IVUS reconstruction were examined with a 30-MHz single-element mechanical transducer (ClearView, CVIS, Boston Scientific Corporation). A constant pullback speed of 0.5 mm/s was used for IVUS image acquisitions. A complete IVUS run was recorded on s-VHS tape for offline 3D reconstruction. At 12 months, IVUS images were also acquired using an ECG-triggered pullback device with a stepping motor at 0.2 mm/step (EchoScan, Tomtec) to assure a precise quantification of neointimal hyperplasia volume. This system acquires images coinciding with the peak of the R wave, eliminating the artifacts caused by the movement of the heart during the cardiac cycle and ultimately improving the quality of image for 3D volumetric quantification. Volumetric IVUS analysis was carried out by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands).[6,7]

Quantitative Measurements

Two coronary segments were subjected to quantitative angiography, in-stent and in-lesion segments. The in-stent analysis encompassed only the 18-mm-long segment covered by the stent. The in-lesion segment was defined as the stent plus 5 mm proximal and 5 mm distal to the edge or the nearest side branch. In-stent and in-lesion restenosis was defined as ≥50% diameter stenosis (DS) at follow-up, located within the stent and target lesion, respectively. Edge restenosis was defined as ≥50% DS at follow-up, located at the proximal or distal edge. Minimal lumen diameter (MLD) and percent DS were calculated for each segment.

Quantitative IVUS analyses of the stent segment were performed at all time points. Lumen and stent boundaries were detected using a minimum-cost algorithm. Total stent and lumen volumes were calculated as previously described. Intimal hyperplasia (IH) volume was calculated as stent volume minus luminal volume. Feasibility, reproducibility, and interobserver and intraobserver variability of these measurements have been validated previously.[8]

Statistical Analysis

Continuous variables are expressed as mean±SD. Comparisons between postintervention and follow-up measurements were performed with a 2-tailed paired t test. Comparisons between groups were performed using unpaired Student's t test. A P value <0.05 was considered statistically significant.

Results

Baseline characteristics were similar between the 3 groups. Overall, 29 patients were male, 32 had stable angina, and 13 were unstable. Mean age was 55.1 (group I), 57.9 (group II) and 60 years (group III). Six patients had a history of diabetes mellitus. Clopidogrel was discontinued at 60 days in all patients.

At the Thoraxcenter, 1 of the 15 patients died on day 2 of a cerebral hemorrhage. She had received abciximab during the procedure and for 12 hours thereafter. Two additional patients (group III) suffered a vessel occlusion during or immediately after the procedure attributable to distal edge dissection and were successfully treated with additional stenting. Subsequent clinical follow-up was uneventful for both patients, and no restenosis was detected at 6-month angiographic follow-up. Finally, 1 asymptomatic patient from Rotterdam refused repeat angiography; thus, 13 completed 6-month angiographic and IVUS follow-up. As reported previously,[2] all patients in groups I and II were discharged without any clinical event. One asymptomatic patient (group II) refused repeat angiography at 12 months.

A representative sequence of angiograms from a single patient are shown in Figure 1. Preprocedure reference vessel diameter (RD) was 2.85±0.46 mm, and postprocedure MLD was 2.47±0.38-mm (in-lesion) and 2.9±0.27-mm (in-stent) in the Rotterdam patients (group III). Four-month data from groups I and II have been reported previously.[2] One-year in-stent MLD (group I, 2.73±0.3 mm; group II, 2.87±0.4 mm) and percent DS (group I, 8.9±6.1%; group II, 6.7±7%) remained essentially unchanged compared with 4-month follow-up. At 6 months (group III), in-stent MLD was 2.66±0.3 mm, and percent DS was 8.9±7.6% (P=NS compared with postprocedure) Changes in in-lesion MLD and percent DS are shown in Figure 2. At 12 months,

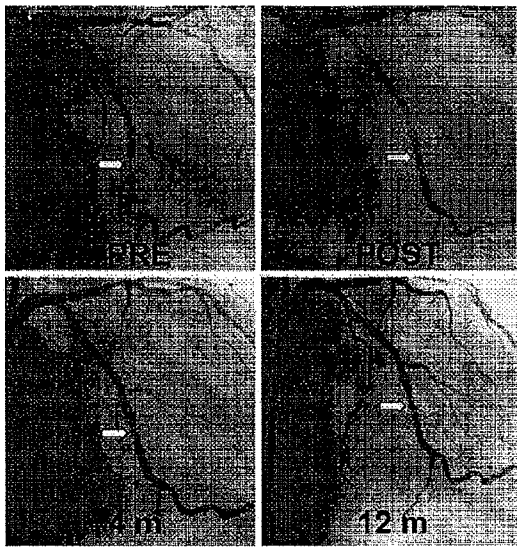

Figure 1. Angiography shows a lesion in the mid portion of the left circumflex marginal branch (white arrow), which was treated with the implantation of a sirolimus-coated BX-velocity stent (top right). Lumen dimensions remained unchanged at 4- and 12- month follow-up (bottom).

in-lesion angiographic lumen dimension showed a small decrease compared with postprocedure in both groups (Figure 2, $P<0.01$). Between 4 months and 12 months, a very small decrease, albeit statically significant ($P=0.004$), in in-lesion MLD was observed in group I. No patient approached the ≥50% DS at 1-year by angiography or IVUS assessment, and no edge restenosis was observed.

At 6-month follow-up, lumen volume was 156.7±63.6 mm^3 (versus 156.5±64.1 mm^3 at postprocedure, P=NS) and intimal hyperplasia volume was 5.7±17.7 mm^3 (group III). Thus, the percent obstruction volume was 2±4.98%, similar to the results reported at 4 months in the patients from São Paulo.[2]

One-year volumetric IVUS data (Figure 3) from the São Paulo patients were actually better than those reported previously at 4-month follow-up.[2] Only 2 patients had >10% IH after 12 months (Figure 3). Differences in the method of volumetric quantification probably explain these findings. As

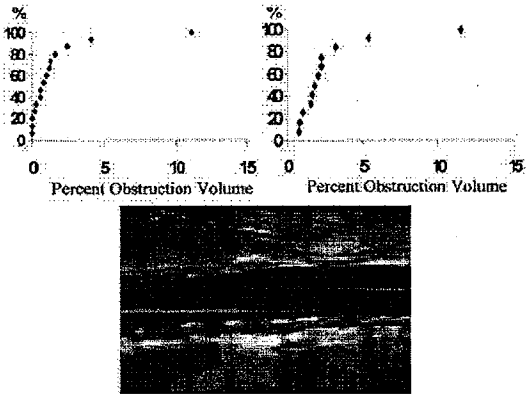

Figure 3. Cumulative distribution curves of percent obstruction volumes in group I (left) and group II (right) at 12-month follow-up. Longitudinal IVUS reconstruction illustrates the virtual absence of in-stent intimal hyperplasia at 12 months (bottom).

a result of the virtual absence of neointimal hyperplasia, the automated contour detection algorithm that was used for the original analysis superimposed the contours of the stent and lumen boundaries in the majority of the cases. Thus, the core laboratory analyst used a "copy and shrink" tool of the quantitative analysis software to dissociate the two contours. This action led to an overestimation of the amount of IH. At 12-month follow-up analysis, the lumen and stent contours were not dissociated artificially, unless IH was clearly visualized. To compare 4-month and 12-month IVUS data, the core laboratory reanalyzed the 4-month IVUS images using the same methodology used at 12 months (Table).

In one patient (group I), 12-month IVUS assessment showed an unstable plaque proximal to the stent. Lesion vulnerability was characterized by positive vessel remodeling and a large lipid pool delimited by a thin fibrous cap (Figure 4). This preexisting plaque increased progressively from the time of the initial procedure, producing a linear deterioration in lumen dimensions (MLD was 2.85 mm postprocedure, 2.51 mm at 4 months, and 2.02 mm at 12 months). No sign of thrombus was detected by angiography or IVUS. At 12 months, the patient was asymptomatic and had a negative stress test. However, at 14-month follow-up, he returned with a non–Q-wave myocardial infarction. Angiography showed

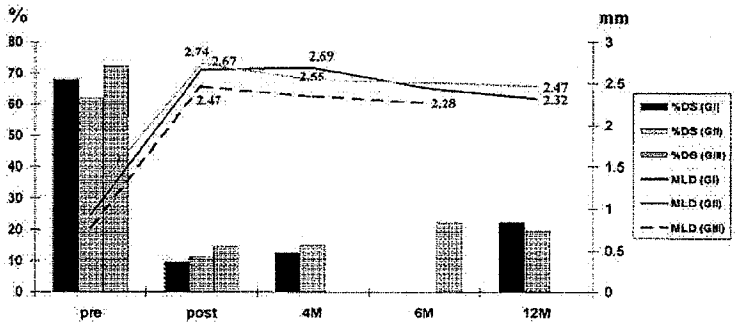

Figure 2. In-lesion percent diameter stenosis (%DS) and MLD over a period of 1 year. Angiographic follow-up was performed at 4 and 12 months in group I (GI) and GII and at 6 months in GIII.

Three-Dimensional Volumetric IVUS Measurements 4 and 12 Months After Implantation of Sirolimus-Eluting Stent

	Stent Volume, mm³		Lumen Volume, mm³		IH Volume, mm³		Obstruction Volume, %	
Follow-up period, mo	4	12	4	12	4	12	4	12
Group I	134±30	127±26	134±30	124±25	0.4±0.8	3.2±8.5	0.3±0.6	2.3±5.5
Group II	138±21	127±30	137±22	124±30	0.3±0.9	2.5±3.4	0.3±0.8	2.2±3.4

No statistical differences were observed between groups or between 4-month and 12-month data within the same group.

the target vessel occluded proximal to the stent, and repeat angioplasty was performed.

The remaining 29 patients of the first 2 cohorts (groups I and II) have now completed 15-month clinical follow-up uneventfully. Similarly, the 14 Rotterdam patients were asymptomatic, with no additional adverse events up to 9 months after the index procedure.

Discussion

The present study demonstrates a potent, long-lasting inhibitory effect on neointimal proliferation exerted by the local release of sirolimus via a stent platform. Regardless of the coating formulation (SR or FR) or population treated (São Paulo or Rotterdam), neointimal hyperplasia, as detected by both angiography and volumetric IVUS quantification, was minimal at all time points (4, 6, or 12 months).

The lack of restenosis observed in this first series of patients treated with sirolimus-eluting Bx VELOCITY stents is probably a consequence of the scaffolding properties of the stent as well as the potent cytostatic effect of sirolimus.[9,10] Like cyclosporin A and tacrolimus (FK506), sirolimus binds to specific cytosolic proteins. However, the mechanism of action of sirolimus is distinct from other immunosuppressive agents that act solely by inhibiting DNA synthesis. The sirolimus:FKBP complex binds to a specific cell-cycle regulatory protein, the mTOR (mammalian target of rapamycin), and inhibits its activation.[11] The inhibition of mTOR induces cell-cycle arrest in late G1 phase.[12–14] The upregulation of FK506-binding protein 12 (FKBP12) observed in human neointimal smooth muscle cells additionally supports the potential antirestenotic effect of sirolimus.[15] Preclinical data have demonstrated the efficacy of both systemic[13,16] and local administration (via drug-eluting stent) (Andrew J. Carter, unpublished data, 2000) of sirolimus in reducing neointimal hyperplasia in different models of restenosis.

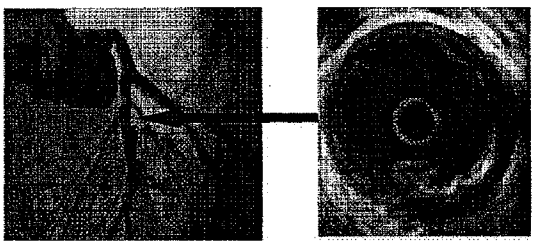

Figure 4. Angiography of the left anterior descending artery showing a nonsignificant stenosis at the proximal edge of the stent (white arrow) at 12-month follow-up. IVUS cross-sectional image at the site of the lesion shows an eccentric plaque with a large lipid pool (L) delimitated by a fibrous cap (arrows). This vessel was occluded 2 months later.

A concern about potential late complications, such as late thrombosis, associated with new therapies is a legacy from our previous experience with intracoronary radiation therapy.[17] In our series, one patient (out of 44) experienced a thrombotic event involving the target coronary artery 14 months after the procedure. It is important to note that IVUS showed an unstable plaque located proximal to the stent that grew progressively in size over the period of observation. The relationship between unstable plaque, as characterized by IVUS, and coronary thrombosis has been reported previously and may explain this unexpected event.[18,19] Experimental investigations have shown a similar degree of re-endothelialization between bare and sirolimus-coated stents occurring as early as 30 days after implantation (Andrew J Carter, unpublished data, 2001), ie, sirolimus does not seem to delay endothelialization. Nevertheless, one cannot completely rule out the possibility of late-stent thrombosis as a cause of vessel occlusion in this case. The occurrence of this somewhat anecdotal event should be interpreted with caution. Data from large randomized multicenter trials, already underway, will be necessary to definitively address this important question.

After our previous study showing a surprising near-absence of IH 4 months after implantation of sirolimus-eluting stents,[2] the logical question was whether this effect would be permanent or whether it merely represented a delay in the proliferative response. The basis for these concerns is the unexpected late-luminal deterioration observed with catheter-based radiation systems and radioactive stents,[1,5] although the mechanisms of action of sirolimus-eluting stents differ considerably from intracoronary brachytherapy. In the present study, angiographic lumen dimensions and IVUS-detected IH volume assessed both at 6-month follow-up (in group III) and at 12 months (groups I and II) was not substantially different from what was observed at 4 months (Table). Thus, at 12-month follow-up, there is no evidence of significant late catch up, and the 12-month IH volume observed in the present study is less than one third of that reported with any previously tested antirestenosis therapy.[6,7] If the findings of the present investigation are confirmed by large, randomized, placebo-controlled trials, this technology is likely to have a major impact on the treatment of coronary artery disease in the near future.

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Comparison of an Everolimus-Eluting Stent and a Paclitaxel-Eluting Stent in Patients With Coronary Artery Disease: A Randomized Trial

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ORIGINAL CONTRIBUTION

Comparison of an Everolimus-Eluting Stent and a Paclitaxel-Eluting Stent in Patients With Coronary Artery Disease

A Randomized Trial

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Context A thin, cobalt-chromium stent eluting the antiproliferative agent everolimus from a nonadhesive, durable fluoropolymer has shown promise in preliminary studies in improving clinical and angiographic outcomes in patients with coronary artery disease.

Objective To evaluate the safety and efficacy of an everolimus-eluting stent compared with a widely used paclitaxel-eluting stent.

Design, Setting, and Patients The SPIRIT III trial, a prospective, randomized, single-blind, controlled trial enrolling patients at 65 academic and community-based US institutions between June 22, 2005, and March 15, 2006. Patients were 1002 men and women undergoing percutaneous coronary intervention in lesions 28 mm or less in length and with reference vessel diameter between 2.5 and 3.75 mm. Angiographic follow-up was prespecified at 8 months in 564 patients and completed in 436 patients. Clinical follow-up was performed at 1, 6, 9, and 12 months.

Interventions Patients were randomized 2:1 to receive the everolimus-eluting stent (n=669) or the paclitaxel-eluting stent (n=333).

Main Outcome Measures The primary end point was noninferiority or superiority of angiographic in-segment late loss. The major secondary end point was noninferiority assessment of target vessel failure events (cardiac death, myocardial infarction, or target vessel revascularization) at 9 months. An additional secondary end point was evaluation of major adverse cardiac events (cardiac death, myocardial infarction, or target lesion revascularization) at 9 and 12 months.

Results Angiographic in-segment late loss was significantly less in the everolimus-eluting stent group compared with the paclitaxel group (mean, 0.14 [SD, 0.41] mm vs 0.28 [SD, 0.48] mm; difference, −0.14 [95% CI, −0.23 to −0.05]; $P \leq .004$). The everolimus stent was noninferior to the paclitaxel stent for target vessel failure at 9 months (7.2% vs 9.0%, respectively; difference, −1.9% [95% CI, −5.6% to 1.8%]; relative risk, 0.79 [95% CI, 0.51 to 1.23]; $P < .001$). The everolimus stent compared with the paclitaxel stent resulted in significant reductions in composite major adverse cardiac events both at 9 months (4.6% vs 8.1%; relative risk, 0.56 [95% CI, 0.34 to 0.94]; $P = .03$) and at 1 year (6.0% vs 10.3%; relative risk, 0.58 [95% CI, 0.37 to 0.90]; $P = .02$), due to fewer myocardial infarctions and target lesion revascularization procedures.

Conclusions In this large-scale, prospective randomized trial, an everolimus-eluting stent compared with a paclitaxel-eluting stent resulted in reduced angiographic late loss, noninferior rates of target vessel failure, and fewer major adverse cardiac events during 1 year of follow-up.

Trial Registration clinicaltrials.gov Identifier: NCT00180479

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By enlarging the arterial lumen and sealing dissection planes, stent implantation relieves coronary flow obstruction at the site of atherosclerotic disease. However, injury to the tunica media results in excessive neointimal hyperplasia in approximately 20% to 30% of patients treated with bare-metal stents, which results in recurrent ischemia often necessitating rehospitalization for repeat percutaneous coronary intervention or coronary artery bypass graft surgery.[1] Drug-eluting stents combine the mechanical scaffolding properties of metallic stents with the site-specific delivery of an antiproliferative agent designed to inhibit vascular responses to arterial injury, thereby reducing restenosis. The polymer-regulated, site-specific delivery of paclitaxel and sirolimus have been shown to inhibit tissue growth after coronary stent implantation and to improve long-term event-free survival compared with bare-metal stents.[2,3] However, restenosis still occurs, and the incidence of stent thrombosis, especially after

For editorial comment see p 1952.

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the first year of implantation, is increased with these drug-eluting stents compared with their bare-metal counterparts,[4,5] likely due to delayed and incomplete endothelialization.[6,7]

Newer drug-eluting stents are being designed with the goal of enhanced safety, efficacy, or both compared with previous devices. Everolimus, a semisynthetic macrolide immunosuppressant, is an analogue of rapamycin, which binds to cytosolic FKBP12 and subsequently to the mammalian target of rapamycin, thereby blocking the stimulatory effects of growth factors and cytokines, which are released after vascular injury. As a result, cell cycle progression is blocked between the G1 and S phases, inhibiting smooth muscle cell proliferation.[8]

Everolimus has been shown to prevent cardiac allograft vasculopathy,[9] which histologically resembles the neointimal hyperplasia that develops after coronary stent implantation.[10] An everolimus-eluting stent has been designed in which the drug is released from a thin (7.8-μm), nonadhesive, durable, biocompatible fluoropolymer coated onto a low-profile (0.0032-in [0.0813-mm] strut thickness), flexible cobalt-chromium stent. Preclinical studies have shown more rapid endothelialization with this stent compared with sirolimus-eluting and paclitaxel-eluting stents.[11] Following favorable results with this device in 1 small and 1 moderate-sized randomized study in Europe,[12,13] the large-scale SPIRIT III trial was performed to evaluate the everolimus-eluting stent in comparison to a widely used paclitaxel-eluting stent in patients with coronary artery disease.

METHODS

Study Population, Device Description, and Protocol

SPIRIT III was a prospective, multicenter, randomized, single-blind, controlled clinical trial in which 1002 patients with either 1 or 2 de novo native coronary artery lesions (maximum 1 lesion per epicardial coronary artery) were randomized in a 2:1 ratio to receive the polymer-based everolimus-eluting stent (XIENCE V; Abbott Vascular, Santa Clara, California) or the polymer-based paclitaxel-eluting stent (TAXUS EXPRESS2; Boston Scientific, Natick, Massachusetts). Patients aged 18 years or older with stable or unstable angina or inducible ischemia undergoing percutaneous coronary intervention were considered for enrollment.

Clinical exclusion criteria included percutaneous intervention in the target vessel either prior to or planned within 9 months after the index procedure; intervention in a nontarget vessel within 90 days prior to or planned within 9 months after the index procedure; prior coronary brachytherapy at any time; acute or recent myocardial infarction with elevated cardiac biomarker levels; left ventricular ejection fraction less than 30%; prior or planned organ transplantation; current or planned chemotherapy for malignancy; known immunologic or autoimmune disease or prescribed immunosuppressive medication; use of chronic anticoagulation; contraindications or allergy to aspirin, heparin, and bivalirudin, thienopyridines, everolimus, cobalt, chromium, nickel, tungsten, acrylic, or fluoropolymers, or to iodinated contrast that cannot be premedicated; elective surgery planned within 9 months after the procedure, necessitating antiplatelet agent discontinuation; platelet count less than 100 000 cells/μL or greater than 700 000 cells/μL, white blood cell count less than 3000 cells/μL, serum creatinine level greater than 2.5 mg/dL (to convert to μmol/L, multiply by 88.4), or dialysis or liver disease; recent major bleeding, hemorrhagic diathesis, or objection to blood transfusions; stroke or transient ischemic attack within 6 months; comorbid conditions that limit life expectancy to less than 1 year or that could affect protocol compliance; positive pregnancy test result, lactation, or planned pregnancy within 1 year after enrollment; and participation in another investigational study that has not yet reached its primary end point. The study was approved by the institutional review board at each participating center, and consecutive, eligible patients signed written informed consent.

Prior to catheterization, an electrocardiogram was performed, creatine phosphokinase and isoenzyme levels were measured, and 300 mg or more of aspirin was administered. A 300-mg or greater oral dose of clopidogrel was recommended preprocedure and required in all cases within 1 hour after stent implantation. Procedural anticoagulation was achieved with either unfractionated heparin or bivalirudin per standard of care, and use of glycoprotein IIb/IIIa inhibitors was per operator discretion. Angiographic eligibility was assessed following mandatory predilatation. The reference vessel diameter of all study lesions was required to be between 2.5 mm and 3.75 mm, and the lesion length was required to be 28 mm or less, both by visual assessment, representing the on-label lesion dimensions for which the paclitaxel-eluting stent has been approved by the US Food and Drug Administration (FDA) for use in the United States. Other angiographic exclusion criteria included ostial or left main lesions; bifurcation lesions with either side branch more than 50% stenosed or more than 2 mm in diameter or requiring predilatation; excessive proximal tortuosity, lesion angulation or calcification, or thrombus; lesion located within a bypass graft conduit; diameter stenosis less than 50% or 100%; or the presence of lesions with greater than 40% stenosis within the target vessel or likelihood that additional percutaneous intervention would be required within 9 months.

Following confirmation of angiographic eligibility, telephone randomization was performed in randomly alternating blocks of 3 and 6 patients using an automated voice response system, stratified by the presence of diabetes, planned dual-vessel treatment, and study site. For this trial everolimus-eluting stents were available in 2.5-, 3.0-, and 3.5-mm diameters, and in 8-, 18-, and 28-mm lengths. The full range of US-manufactured paclitaxel-eluting stents were available, ranging from 2.5 to 3.5 mm in diameter and from 8 to 32 mm in length. An appropriate-length stent was selected sufficient to cover approximately 3 mm of nondiseased tissue on either side of the lesion. In patients receiving multiple

stents for a single lesion, 1 to 4 mm of stent overlap was recommended. Additional study stents were permitted for edge dissections greater than type C or otherwise suboptimal results, and postdilation was at operator discretion.

Following the procedure, an electrocardiogram was performed and cardiac enzyme levels were measured. The protocol recommended that patients receive aspirin (≥80 mg/d) indefinitely and clopidogrel (75 mg/d) for a minimum of 6 months. Clinical follow-up was scheduled at 30 (±7) days, 180 (±14) days, 240 (±28) days, 270 (±14) days, 365 (±28) days, and then yearly (±28 days) through 5 years. Although the operators were by necessity unblinded during the stent implantation procedure, the patient and staff involved in follow-up assessments remained blinded through the follow-up period, with a standardized follow-up interview script used to reduce bias. Protocol-specified angiographic follow-up was scheduled at 240 (±28) days in the first 564 patients enrolled. Among these patients, intravascular ultrasound immediately following stent implantation and at follow-up was intended in 240 patients at selected sites.

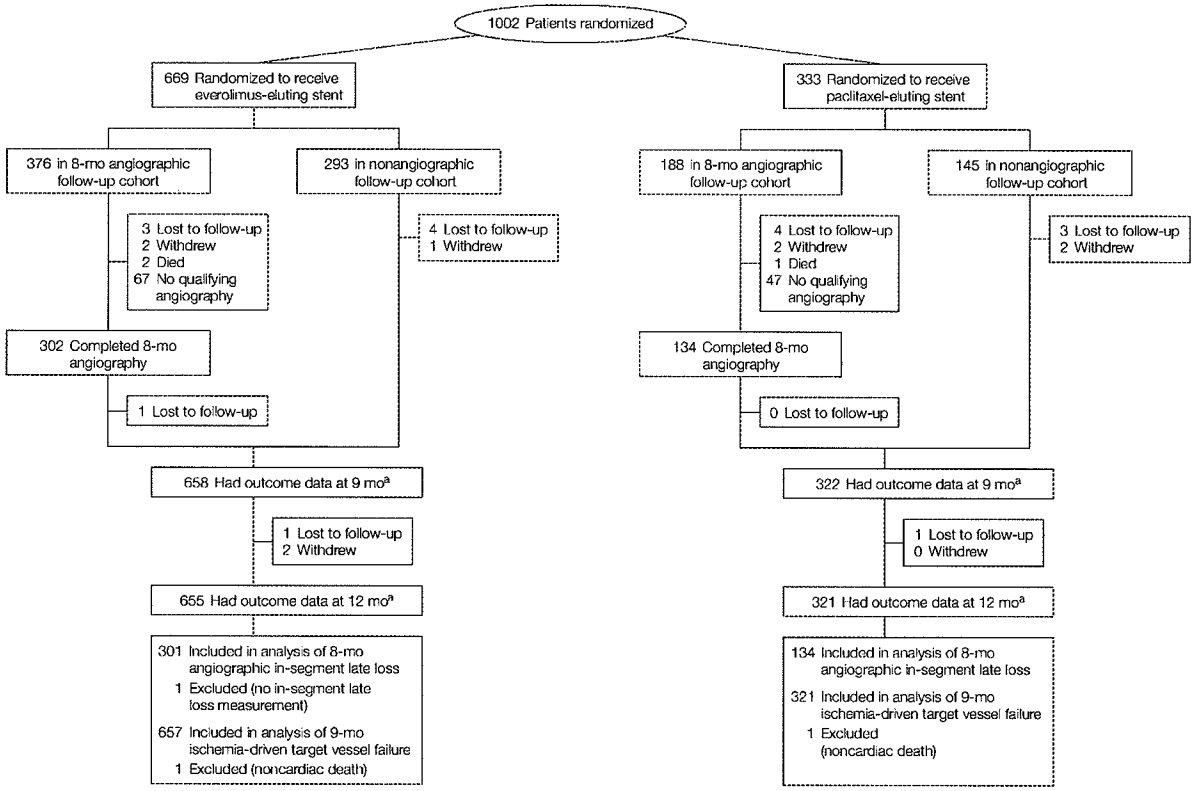
Data Management

Independent study monitors verified 100% of case report form data on-site. Data were stored in a database maintained by Abbott Vascular. All major adverse cardiac events were adjudicated by an independent committee blinded to treatment allocation after review of original source documentation. A second clinical events committee blinded to randomization performed a post hoc adjudication of stent thrombosis using the Academic Research Consortium definitions.[14] A data and safety monitoring board periodically reviewed blinded safety data, each time recommending that the study continue without modification. Independent core angiographic and intravascular ultrasound analyses were performed by technicians blinded to treatment assignment and clinical outcomes using validated methods as previously described.[15,16]

End Points and Definitions

The primary end point was in-segment late loss at 240 days (defined as the difference in the minimal luminal diameter assessed immediately after the pro-

Figure 1. Patient Flow and Follow-up in the SPIRIT III Trial



Prior to the 1-year follow-up period, 14 of 669 patients (2.1%) randomized to receive the everolimus-eluting stent either withdrew (n=5) or were lost to follow-up (n=9), and 12 of 333 patients (3.6%) randomized to receive the paclitaxel-eluting stent either withdrew (n=4) or were lost to follow-up (n=8).
[a]Nine-month follow-up was performed at 270 (±14) days; 12-month follow-up, at 365 (±28) days.

Table 1. Baseline Characteristics of the Study Population

Characteristic	Everolimus-Eluting Stent	Paclitaxel-Eluting Stent
Demographics, No./total (%)	669	332
Age, mean (SD), y	63.2 (10.5)	62.8 (10.2)
Men	469/669 (70.1)	218/332 (65.7)
Hypertension	510/669 (76.2)	245/331 (74.0)
Hypercholesterolemia	489/659 (74.2)	233/326 (71.5)
Diabetes mellitus		
Any	198/669 (29.6)	92/330 (27.9)
Requiring insulin	52/669 (7.8)	18/330 (5.5)
Current smoker	154/659 (23.4)	73/324 (22.5)
Prior myocardial infarction	130/652 (19.9)	59/327 (18.0)
Unstable angina	123/657 (18.7)	82/327 (25.1)
Target vessel, No./total (%)	772	383
Left anterior descending	317/768 (41.3)	164/382 (42.9)
Left circumflex	212/768 (27.6)	108/382 (28.3)
Right coronary	238/768 (31.0)	109/382 (28.5)
Left main, protected	1/768 (0.1)	1/382 (0.3)
Target lesion, mean (SD)	772	383
Reference vessel diameter, mm	2.77 (0.45)	2.76 (0.46)
Minimal luminal diameter, mm	0.82 (0.41)	0.83 (0.40)
Diameter stenosis, %	70.0 (13.3)	69.4 (13.6)
Lesion length, mm	14.7 (5.6)	14.7 (5.7)

cedure and at angiographic follow-up, measured within the margins, 5 mm proximal and 5 mm distal to the stent). To avoid interlesion clustering of restenosis in patients receiving stents for multiple lesions[17] (which would have required correction with multilevel generalized estimating equations), the protocol specified that for patients in whom 2 lesions were treated a single lesion (the analysis lesion) would be randomly selected by computer for analysis of late loss. All randomized lesions were included in the analyses for all other angiographic end points.

The major secondary end point was ischemia-driven target vessel failure at 270 days, defined as the composite of cardiac death (death in which a cardiac cause could not be excluded), myocardial infarction (Q-wave or non–Q-wave), and ischemia-driven target vessel revascularization by either percutaneous coronary intervention or bypass graft surgery. Target vessel (or lesion) revascularization was considered to be ischemia-driven if associated with a positive functional study result, a target vessel (or lesion) diameter stenosis of 50% or greater by core laboratory quantitative analysis with ischemic symptoms, or a target vessel (or lesion) diameter stenosis of 70% or greater with or without documented ischemia.

An additional prespecified secondary end point included major adverse cardiac events at 9 months and 1 year, defined as the composite of cardiac death, myocardial infarction, or ischemia-driven target lesion revascularization. Myocardial infarction was defined either as the development of new pathologic Q waves 0.4 seconds or longer in duration in 2 or more contiguous leads or as an elevation of creatine phosphokinase levels to more than 2 times normal with positive levels of creatine phosphokinase MB. Stent thrombosis was prospectively defined by protocol as an acute coronary syndrome with angiographic evidence of thrombus within or adjacent to a previously treated target lesion or, in the absence of angiography, as any unexplained death or acute myocardial infarction with ST-segment elevation or new Q waves in the distribution of the target lesion occurring within 30 days. Binary restenosis was defined as 50% or greater diameter stenosis of the treated lesion at angiographic follow-up. Other angiographic and intravascular ultrasound parameters were defined as previously described.[15,16]

Statistical Methods

The trial was powered for noninferiority for both the primary end point of in-segment late loss at 8 months among patients in the angiographic follow-up cohort, as well as the major secondary end point of ischemia-driven target vessel failure at 9 months in all enrolled patients. As agreed on with FDA, noninferiority for in-segment late loss would be declared if the upper limit of the 1-sided 97.5% confidence interval (CI) of the difference did not exceed a delta of 0.195 mm from the observed in-segment late lumen loss in the paclitaxel-eluting stent group, equivalent to a 1-sided test with $\alpha = .025$. Assuming a mean late loss of 0.24 (SD, 0.47) mm for both stents, with angiographic follow-up performed in 338 everolimus-eluting stent and 169 paclitaxel-eluting stent analysis lesions, the trial had 99% power to demonstrate noninferiority for in-segment late loss. Sequential superiority testing was prespecified if noninferiority for late loss was met. Noninferiority for ischemia-driven target vessel failure was declared if the upper limit of the 1-sided 95% CI of the difference did not exceed a delta of 5.5% from the observed paclitaxel-eluting stent control event rate. Assuming a target vessel failure rate of 9.4% for both stents, with 9-month clinical follow-up performed in 660 patients randomized to receive the everolimus-eluting stent and 330 to receive the paclitaxel-eluting stent, the trial had 89% power to demonstrate noninferiority for target vessel failure. Noninferiority for the prespecified powered primary as well as the major secondary end points had to be met for the trial to be considered successful, and as such both are considered coprimary end points.

Categorical variables were compared by Fisher exact test. Continuous variables are presented as mean (SD) and were compared by *t* test. The statistical analysis plan prespecified that all primary and secondary analyses

would be performed in the intent-to-treat population, consisting of all patients randomized in the study, regardless of the treatment actually received. However, patients lost to follow-up in whom no event had occurred prior to the follow-up windows were not included in the denominator for calculations of binary end points. Survival curves using all available follow-up data were also constructed for time-to-event variables using Kaplan-Meier estimates and compared by log-rank test. Superiority testing was performed after demonstration of noninferiority for the primary and major secondary end points[18] and for all other secondary end points using a 2-sided $\alpha = .05$. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patients and Enrollment

Between June 22, 2005, and March 15, 2006, 1002 patients were enrolled at 65 US sites and randomized to receive the everolimus-eluting stent (n=669) or the paclitaxel-eluting stent (n=333) (FIGURE 1). One patient in the paclitaxel group did not sign informed consent; thus, his or her data are unavailable. Baseline characteristics of the patients were well matched between the 2 groups (TABLE 1), except for slightly more unstable angina in the paclitaxel group (P=.02). The mean number of lesions stented was 1.2 (SD, 0.4) in each group; 2 lesions were treated in 15.4% of patients in each group, whereas the remainder had 1 lesion treated. Lesion characteristics as measured by quantitative coronary angiography were also similar between the 2 groups (Table 1).

Procedural Results and Angiographic Outcomes

As shown in TABLE 2, the total stent length per lesion was slightly greater in the everolimus group, likely due to the fewer stent lengths available for accurate lesion matching. Conversely, implantation pressure was slightly less in the group receiving everolimus stents. Other procedural variables were well matched between the groups. Acute postprocedure angiographic measures were also not significantly different between the 2 groups.

Angiographic follow-up at 8 months was completed in 77% of eligible patients (Figure 1). The primary end point of in-segment late loss in the analysis lesion was significantly less in the everolimus group compared with the paclitaxel group (0.14 [SD, 0.41] mm [n=301 lesions] vs 0.28 [SD, 0.48] mm [n=134 lesions]; difference, −0.14 [95% CI, −0.23 to −0.05]; $P_{\text{noninferiority}} < .001$; $P_{\text{superiority}} = .004$). In-stent late loss in the analysis lesion was also significantly less in the everolimus group (0.16 [SD, 0.41] mm vs 0.31 [SD, 0.55] mm; difference, −0.15 [95% CI, −0.25 to −0.04]; $P_{\text{noninferiority}} < .001$; $P_{\text{superiority}} = .006$). Similar results were found when all lesions were considered (Table 2). As a result, strong trends were present toward a reduction in binary in-stent and in-segment restenosis with the everolimus stent compared with the paclitaxel stent (Table 2). No aneurysms were present at 8 months in either group.

Intravascular Ultrasound Findings

Volumetric intravascular ultrasound data were available at 8 months in 101

Table 2. Procedural Results and Angiographic Outcomes

Result/Outcome	Everolimus-Eluting Stent	Paclitaxel-Eluting Stent	*P* Value
Procedural variables, mean (SD)			
No. of patients	669	332	
No. of stents per patient	1.3 (0.6)	1.3 (0.5)	.27
No. of stents per lesion	1.2 (0.4)	1.1 (0.3)	.07
Maximum stent diameter per lesion, mm	3.0 (0.4)	3.0 (0.4)	>.99
Maximum stent to reference vessel diameter ratio	1.1 (0.1)	1.1 (0.1)	.56
Total stent length per lesion, mm	22.8 (8.4)	21.6 (7.8)	.02
Total stent to lesion length ratio	1.6 (0.5)	1.5 (0.5)	.01
Maximum pressure, atm	14.8 (2.9)	15.1 (2.6)	.049
Glycoprotein IIb/IIIa inhibitors used, No./total (%)	184/669 (27.5)	82/332 (24.7)	.36
Postprocedural angiographic results, mean (SD)			
No. of lesions	772	383	
Minimal luminal diameter, mm			
In-stent	2.71 (0.43)	2.74 (0.41)	.38
In-segment	2.37 (0.45)	2.36 (0.45)	.73
Diameter stenosis, %			
In-stent	0.3 (8.9)	−0.2 (9.9)	.37
In-segment	13.5 (7.6)	14.4 (7.1)	.06
Acute gain, mm			
In-stent	1.89 (0.48)	1.91 (0.47)	.56
In-segment	1.54 (0.51)	1.53 (0.50)	.62
8-mo angiographic follow-up, mean (SD)[a]			
No. of lesions	344	158	
Reference vessel diameter, mm	2.77 (0.43)	2.78 (0.42)	.84
Minimal luminal diameter, mm			
In-stent	2.56 (0.53)	2.45 (0.65)	.07
In-segment	2.22 (0.53)	2.12 (0.60)	.08
Diameter stenosis, %			
In-stent	5.9 (16.4)	10.3 (21.4)	.02
In-segment	18.8 (14.4)	22.8 (16.4)	.008
Late loss, mm			
In-stent	0.16 (0.41)	0.30 (0.53)	.002
In-segment	0.14 (0.39)	0.26 (0.46)	.003
Binary restenosis, No./total (%)			
In-stent	8/343 (2.3)	9/158 (5.7)	.06
In-segment	16/344 (4.7)	14/158 (8.9)	.07

[a] Analysis of all lesions.

lesions in the everolimus group and 41 in the paclitaxel group. The everolimus stent compared with the paclitaxel stent resulted in significantly less neointimal hyperplasia (10.13 [SD, 11.46] mm^3 vs 20.87 [SD, 31.51] mm^3, $P=.04$) and percent volume obstruction (6.9% [SD, 6.4%] vs 11.2% [SD, 9.9%], $P=.01$). Paired immediate postprocedure and follow-up intravascular ultrasound studies were available in 90 lesions in the everolimus group and 43 in the paclitaxel group. Comparing the everolimus and paclitaxel stents, there were no significant differences detected in the rates of incomplete stent apposition either at the completion of the procedure (34.4% vs 25.6%, respectively; $P=.33$) or at 8 months (25.6% vs 16.3%, $P=.27$). Late acquired incomplete stent apposition was infrequent in both groups (1.1% vs 2.3%, $P=.54$).

Clinical Outcomes

At 30 days there tended to be fewer myocardial infarctions among the patients randomized to receive the everolimus stent compared with the paclitaxel stent (7/667 patients [1.0%] vs 9/330 [2.7%], respectively; relative risk, 0.38 [95% CI, 0.14 to 1.02]; $P=.06$), with comparable rates of cardiac death (0% in both groups) and target lesion revascularization (3/667 patients [0.4%] vs 1/330 [0.3%], respectively; relative risk, 1.48 [95% CI, 0.15 to 14.21]; $P>.99$). At 9 months, everolimus stents compared with paclitaxel stents were noninferior for the major secondary end point of ischemia-driven target vessel failure (47/657 patients [7.2%] vs 29/321 [9.0%], respectively; difference, −1.9% [95% CI, −5.6% to 1.8%]; relative risk, 0.79 [95% CI, 0.51 to 1.23]; $P_{noninferiority}<.001$; $P_{superiority}=.31$). A nonsignificant trend was also present at 1 year for a 24% reduction in target vessel failure in patients randomized to receive everolimus stents rather than paclitaxel stents (56/653 patients [8.6%] vs 36/320 [11.3%], respectively; relative risk, 0.76 [95% CI, 0.51 to 1.13]; $P=.20$). Use of the everolimus stent compared with the paclitaxel stent resulted in significant reductions in the secondary end point of composite major adverse cardiac events, both at 9 months (30/657 patients [4.6%] vs 26/321 [8.1%]; relative risk, 0.56 [95% CI, 0.34 to 0.94]; $P=.03$) and at 1 year (39/653 patients [6.0%] vs 33/320 [10.3%]; relative risk, 0.58 [95% CI, 0.37 to 0.90]; $P=.02$).

As shown in TABLE 3, there were no significant differences between the everolimus stent and the paclitaxel stent in the 1-year rates of death (all cause, cardiac, or noncardiac) or of myocardial infarction (all, Q-wave, or non–Q-wave). Similarly, there were no significant differences between the 2 devices in the rates of stent thrombosis, either early (≤30 days) or late (>30 days), whether analyzed by the prespecified protocol definition or by post hoc Academic Research Consortium definitions. There were also no statistically significant differences in the rates of target lesion revascularization, target vessel revascularization, or target vessel failure between the 2 stents at 1 year. As shown in FIGURE 2, the difference between the hazard curves for major adverse cardiac events became apparent in the early postprocedural period due to fewer myocardial infarctions with the everolimus stent, and then spread further between 6 and 12 months due to fewer target lesion revascularization procedures with the everolimus stent. Of the 15 and 12 patients in the everolimus and paclitaxel groups who had a protocol-defined ischemic target lesion revascularization event by 1 year, 5 and 4 patients, respectively (33.3% in each group) underwent revascularization solely on the basis of a diameter stenosis greater than 70% demonstrated by quantitative coronary angiography. At 365 days, aspirin was being taken by 94.9% and 92.4%

Table 3. Clinical Outcomes at 1 Year

Outcome	No./Total (%) Everolimus-Eluting Stent (n = 655)	No./Total (%) Paclitaxel-Eluting Stent (n = 321)	*P* Value
Death	8/655 (1.2)	4/321 (1.2)	>.99
Cardiac	5/655 (0.8)	3/321 (0.9)	.72
Noncardiac	3/655 (0.5)	1/321 (0.3)	>.99
Myocardial infarction[a]	18/653 (2.8)	13/320 (4.1)	.33
Q-wave	2/653 (0.3)	1/320 (0.3)	>.99
Non–Q-wave	16/653 (2.5)	12/320 (3.8)	.31
Death or myocardial infarction	24/654 (3.7)	16/321 (5.0)	.39
Cardiac death or myocardial infarction[a]	22/653 (3.4)	15/320 (4.7)	.37
Stent thrombosis			
Protocol definition	5/647 (0.8)	2/317 (0.6)	>.99
≤30 d	3/667 (0.4)	0/330 (0)	.55
>30 d	2/646 (0.3)	2/317 (0.6)	.60
ARC			
Definite	5/652 (0.8)	0/319 (0)	.18
Probable	2/652 (0.3)	2/319 (0.6)	.60
Possible	4/652 (0.6)	2/319 (0.6)	>.99
Definite or probable	7/652 (1.1)	2/319 (0.6)	.73
Any	11/652 (1.7)	4/319 (1.3)	.78
Target lesion revascularization	22/655 (3.4)	18/321 (5.6)	.12
Target vessel revascularization	40/655 (6.1)	24/321 (7.5)	.41
Target vessel revascularization remote	20/655 (3.1)	14/321 (4.4)	.35
Major adverse cardiac events[a]	39/653 (6.0)	33/320 (10.3)	.02
Target vessel failure[a]	56/653 (8.6)	36/320 (11.3)	.20

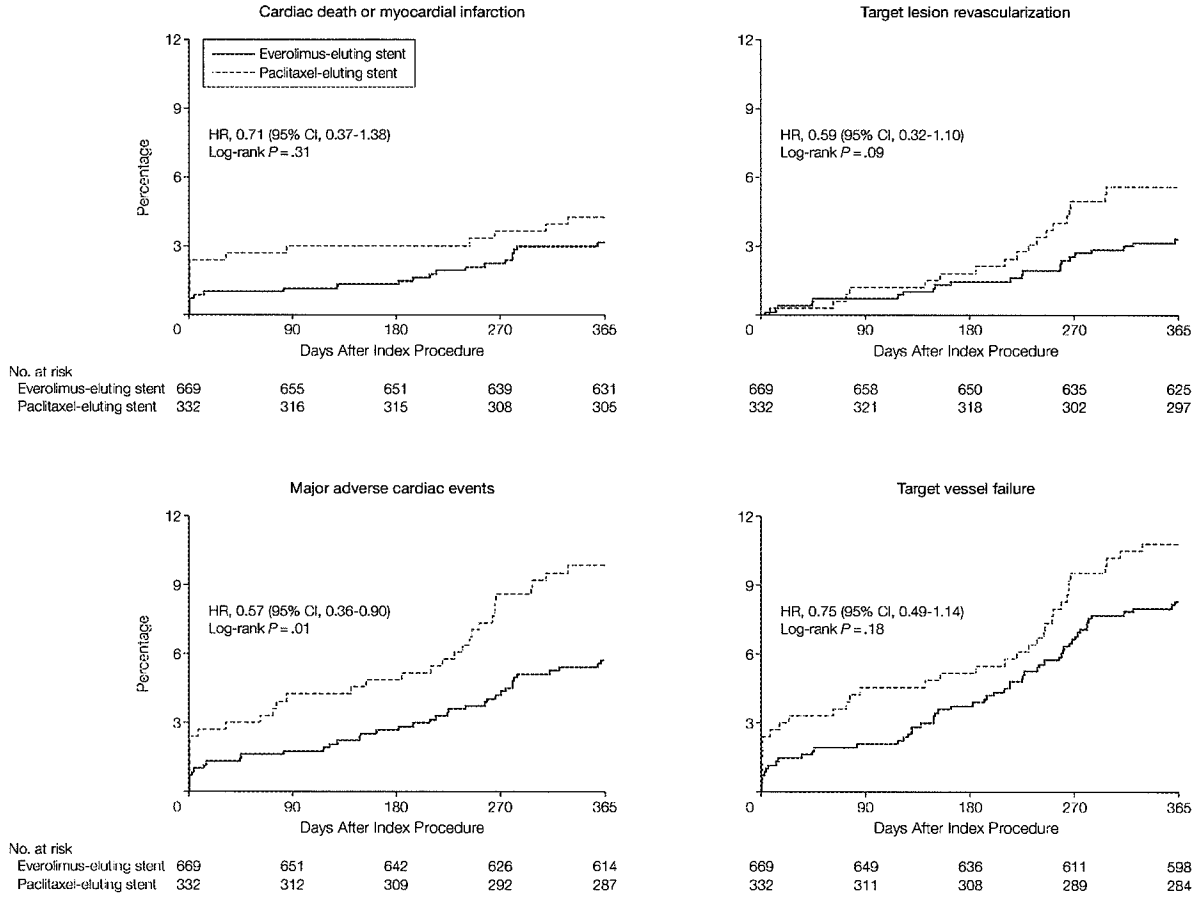
Abbreviations: ARC, Academic Research Consortium.[14]
[a] Per the statistical analysis plan, since the composite target vessel failure and major adverse cardiac event end points included cardiac deaths only, patients with noncardiac deaths were excluded from the denominator.

of patients receiving everolimus stents and paclitaxel stents, respectively (P=.15), and a thienopyridine (clopidogrel or ticlopidine) was being taken by 71.2% and 70.4%, respectively (P=.82).

Subgroup Analysis

A post hoc linear regression analysis with formal interaction testing was performed to explore whether the reduction of the primary end point of in-segment late loss at 8 months with the everolimus stent compared with the paclitaxel stent was consistent across important subgroups (of which diabetes and the number of treated vessels were prespecified). As shown in FIGURE 3, there were no significant interactions between treatment assignment and angiographic outcomes among 7 subgroups, with the exception of age. Logistic regression analysis with interaction testing was also performed to explore whether the reduction in major adverse cardiac events with the everolimus stent compared with the paclitaxel stent present at 1 year was consistent across important subgroups. As shown in FIGURE 4, there were no significant interactions between treatment assignment and outcomes at 1 year among 8 subgroups, with the exception of patients with diabetes. The relative reduction in major adverse cardiac events with everolimus stents compared with paclitaxel stents was comparable in patients both undergoing and not undergoing 8-month follow-up angiography. Among patients in the angiographic follow-up cohort, target lesion revascularization in the everolimus and paclitaxel stent groups was required in 15 of 368 (4.1%) vs 12 of 181 (6.6%) patients, respectively (relative

Figure 2. Time-to-Event Curves for Cardiac Death or Myocardial Infarction, Target Lesion Revascularization, Major Adverse Cardiac Events, and Target Vessel Failure Among Patients Randomized to Receive the Everolimus-Eluting Stent and the Paclitaxel-Eluting Stent



Event rates presented here were calculated by Kaplan-Meier methods and compared with the log-rank test and differ slightly from those in the text and Table 3, which were calculated as categorical variables and compared with the Fisher exact test. In each panel, initial number at risk for the paclitaxel stent differs from the number randomized because 1 patient did not sign informed consent. CI indicates confidence interval; HR, hazard ratio.

risk, 0.61 [95% CI, 0.29 to 1.29]; P=.21), whereas in the nonangiographic follow-up cohort the target lesion revascularization rates were 7 of 285 (2.5%) vs 6 of 139 (4.3%), respectively (relative risk, 0.57 [95% CI, 0.19 to 1.66]; P=.37).

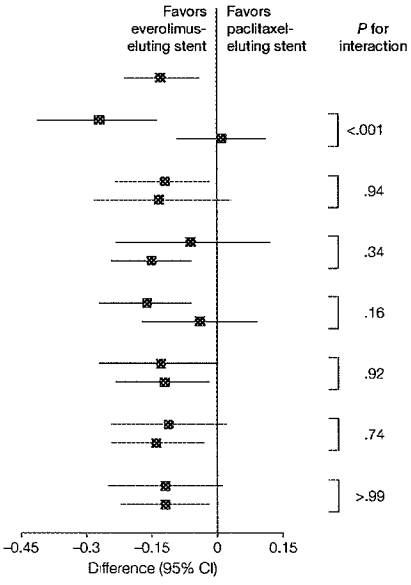
COMMENT

This large-scale, prospective, randomized, single-blind, controlled study demonstrates that an everolimus-eluting stent compared with a widely used paclitaxel-eluting stent results in a significant reduction in angiographic in-segment late loss at 8 months, with noninferior 9-month rates of ischemia-driven target vessel failure. Thus, the 2 prespecified FDA regulatory requirements required for the trial to be considered successful were met. The reduction in late loss was confirmed by the findings from intravascular ultrasound, which demonstrated an approximate 50% reduction in volumetric neointimal hyperplasia. As a result, even though the trial was not powered for a reduction in binary angiographic restenosis, a strong trend was present in this direction favoring the everolimus-eluting stent.

Notably, the everolimus stent compared with the paclitaxel stent resulted in a significant 42% reduction in major adverse cardiac events at 1 year. As such, the present study is the first pivotal randomized trial to demonstrate enhanced event-free survival with a new stent compared with any of the 3 drug-eluting stents commercially available in the United States for on-label lesions (ie, those for which treatment with drug-eluting stents has been approved by the FDA). As defined in this trial, major adverse cardiac events is a composite measure of safety (cardiac death and myocardial infarction) and stent efficacy (target lesion revascularization), which is more specific to the action of the stent than is target vessel failure (which includes the occurrence of target vessel revascularization remote from the target lesion, which would not be expected to be affected by stent implantation). The reduction in composite major adverse cardiac events with the everolimus stent was attributable to fewer postprocedural non–Q-wave myocardial infarctions and late target lesion revascularizations due to the reduction in restenosis. In this regard the results of SPIRIT III confirm and extend those from the smaller (300 patients) randomized SPIRIT II trial, in which the 1-year rates of major adverse cardiac events (using the same definition) were decreased from 9.2% with a paclitaxel-eluting stent to 2.7% with an everolimus-eluting stent (P=.04), also due to fewer cardiac deaths, myocardial infarctions, and target lesion revascularizations.[19] Reduction in procedural-related myonecrosis with the everolimus stent may result from less side-branch compromise due to the thinner polymer (7.8 μm vs 16.0 μm) and total polymer plus stent strut width (89 vs 148 μm) compared with the paclitaxel stent,[20] though detailed angio-

Figure 3. Subgroup Analyses of the Primary End Point of 8-Month Angiographic In-Segment Late Loss Among Patients Randomized to Receive the Everolimus-Eluting Stent vs the Paclitaxel-Eluting Stent

	No. of randomized lesions		In-segment luminal late loss, mean (SD), mm				
	Everolimus-eluting stent	Paclitaxel-eluting stent	Everolimus-eluting stent	Paclitaxel-eluting stent	Difference (95% CI)	Favors everolimus-eluting stent	Favors paclitaxel-eluting stent	*P* for interaction
Angiographic follow-up cohort	343	158	0.14 (0.39)	0.26 (0.46)	−0.13 (−0.21 to 0.04)			
Age								
≥Median (63 y)	171	76	0.12 (0.37)	0.39 (0.55)	−0.27 (−0.41 to 0.14)			<.001
<Median	172	82	0.16 (0.42)	0.15 (0.33)	0.01 (−0.09 to 0.11)			
Sex								
Men	250	108	0.13 (0.34)	0.25 (0.49)	−0.12 (−0.23 to −0.02)			.94
Women	93	50	0.16 (0.51)	0.29 (0.41)	−0.13 (−0.28 to 0.03)			
Diabetes								
Yes	96	31	0.18 (0.51)	0.24 (0.40)	−0.06 (−0.23 to 0.12)			.34
No	247	127	0.12 (0.34)	0.27 (0.48)	−0.15 (−0.24 to −0.06)			
No. of treated vessels								
Single	258	110	0.13 (0.41)	0.30 (0.49)	−0.16 (−0.27 to −0.06)			.16
Dual	85	48	0.14 (0.33)	0.18 (0.39)	−0.04 (−0.17 to 0.09)			
Target vessel								
LAD	135	68	0.13 (0.40)	0.26 (0.49)	−0.13 (−0.27 to 0.00)			.92
Non-LAD	208	90	0.14 (0.39)	0.26 (0.45)	−0.12 (−0.23 to −0.02)			
RVD								
>Median (2.775 mm)	166	88	0.18 (0.38)	0.29 (0.54)	−0.11 (−0.24 to 0.02)			.74
≤Median	177	70	0.10 (0.41)	0.24 (0.36)	−0.14 (−0.24 to −0.03)			
Lesion length								
>Median (13.7 mm)	169	82	0.19 (0.47)	0.31 (0.51)	−0.12 (−0.25 to 0.01)			>.99
≤Median	174	74	0.09 (0.30)	0.21 (0.40)	−0.12 (−0.22 to −0.02)			

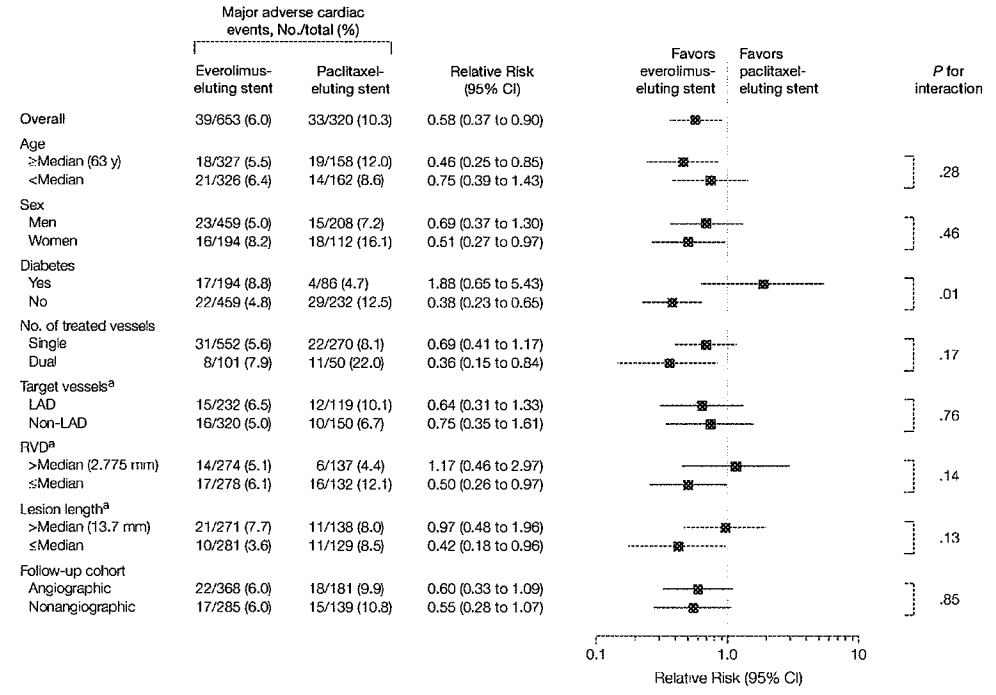


Probability for interaction represents the likelihood for interaction between the variable and the relative treatment effect. CI indicates confidence interval; LAD, left anterior descending; RVD, reference vessel diameter.

graphic study is required to confirm this possibility. Importantly, there were no significant differences in the occurrence of stent thrombosis through 1 year between these 2 devices, though this trial was underpowered to reliably evaluate this event; also, longer-term follow-up is required, because the incremental risk of stent thrombosis with drug-eluting stents may emerge beyond 1 year.[4] The lower rate of target lesion revascularization with the everolimus stent compared with the paclitaxel stent may be directly attributed to the reduction in late loss and smaller follow-up diameter stenosis in the target lesion, as recently described.[21]

The reduction in in-segment late loss with the everolimus stent compared with the paclitaxel stent was consistent across multiple important subgroups except when stratified by age. No significant differences in angiographic outcomes were present between the 2 stents in young patients, whereas assignment to receive the everolimus stent rather than the paclitaxel stent was associated with a marked reduction in late loss in elderly patients. Given the lack of an interaction with reference vessel diameter and lesion length, an explanation underlying this finding is not immediately evident. Of note, no interaction was present between diabetic status and angiographic late loss, signifying a significant reduction in in-segment late loss with the everolimus stent compared with the paclitaxel stent in patients both with and without diabetes. In contrast, a significant interaction was present between diabetes and stent type on the major adverse cardiac event end point, a finding that contributes to the conflicting reports from prior studies examining the relative safety and efficacy of paclitaxel-eluting compared with sirolimus-eluting stents in patients with diabetes.[22-25] However, this difference was driven by the 62% lower rate of major adverse cardiac events in patients with diabetes who were treated with paclitaxel stents compared with patients without diabetes who also were treated with paclitaxel stents, an unlikely finding that may have been due to chance alone. The differences between the 2 devices were also less apparent in larger vessels (which, compared with small vessels, may be able to accommodate more neointimal hyperplasia before the ischemic threshold is reached)[21] and in longer lesions (which, compared with shorter lesions, may have a greater statistical likelihood of restenosis developing in a

Figure 4. Subgroup Analyses of the 1-Year Rates of Major Adverse Cardiac Events Among Patients Randomized to Receive the Everolimus-Eluting Stent vs the Paclitaxel-Eluting Stent



Probability for interaction represents the likelihood for interaction between the variable and the relative treatment effect. CI indicates confidence interval; LAD, left anterior descending; RVD, reference vessel diameter.
[a]Analysis restricted to patients undergoing treatment of a single lesion.

single spot, despite less volumetric neointimal hyperplasia). Moreover, no differences were evident in the beneficial effect of the everolimus stent compared with the paclitaxel stent in reducing the occurrence of major adverse cardiac events as a function of age. All of these subgroup findings should be considered hypothesis-generating, because subgroup analysis is inherently underpowered and statistical adjustments were not made for multiple comparisons leading to possible false-positive findings.[26]

The strengths and limitations of the present investigation should be considered. That composite major adverse cardiac events have now been shown to be reduced with an everolimus stent compared with a paclitaxel stent in 2 consecutive randomized trials performed at different institutions in different geographies (United States vs Europe and Asia Pacific)[19] increases the likelihood that this finding is real. Despite the dilutive effect of including target vessel revascularization in the target vessel failure end point, a trend was also present toward a 24% reduction with the everolimus stent in this composite measure at 1 year. Moreover, the clinical and angiographic outcomes with the paclitaxel stent in the present study were similar or better than those observed in earlier trials with this device in comparable patients and lesions,[2] and as such underperformance of the control stent does not explain this finding. However, while SPIRIT III is the largest completed trial to date investigating an everolimus-eluting stent, major adverse cardiac events were not the primary end point of this study (nor of SPIRIT II), and therefore this conclusion cannot be considered definitive until prospectively verified in an adequately powered randomized trial. The present trial also was underpowered to examine whether an everolimus stent reduces target lesion revascularization, target vessel revascularization, and target vessel failure as well as the occurrence of low-frequency safety events, compared with a paclitaxel stent. That angiographic follow-up was performed in 43.5% of patients in the present trial further raises concern whether the greater late loss with the paclitaxel stent compared with the everolimus stent may have triggered a greater proportion of excess revascularization procedures in the former group (the "oculostenotic reflex"),[27] although such a bias was not apparent in subgroup analysis. Logistic considerations precluded blinding the operator to the stent type, although clinical follow-up assessment, core laboratory, and clinical events committee personnel were blinded to randomization group, and source-documented ischemia or a severe stenosis by quantitative analysis was required to be present for declaration of target lesion or vessel revascularization. The results of the present trial cannot be extended to patient and lesion types excluded from enrollment. Also, complete screening log data are not available, and thus the proportion of patients undergoing percutaneous coronary intervention who were eligible for enrollment in this study is unknown. Finally, the current study was not designed to elicit other potential advantages of the everolimus stent, such as its greater flexibility and deliverability in complex coronary anatomy.

In summary, in this large-scale, prospective randomized trial, an everolimus-eluting stent compared with a paclitaxel-eluting stent in de novo native coronary artery lesions resulted in reduced angiographic late loss, noninferior rates of target vessel failure, and fewer major adverse cardiac events during 1 year of follow-up.

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Independent Statistical Analysis: The accuracy of the data analysis was independently verified by Martin Fahy, MSc, from the Cardiovascular Research Foundation (CRF), an affiliate of Columbia University College of Physicians and Surgeons. (The dean of Columbia University is responsible for this collaboration with the CRF and empowers an active oversight committee to monitor this relationship and the activities of the CRF.) Mr Fahy received the entire raw database and replicated all of the analyses that were reported in the manuscript, and no discrepancies were discovered. The results reported in this article are the results based on this independent analysis. Neither Mr Fahy nor the CRF received any funding for this independent analysis.

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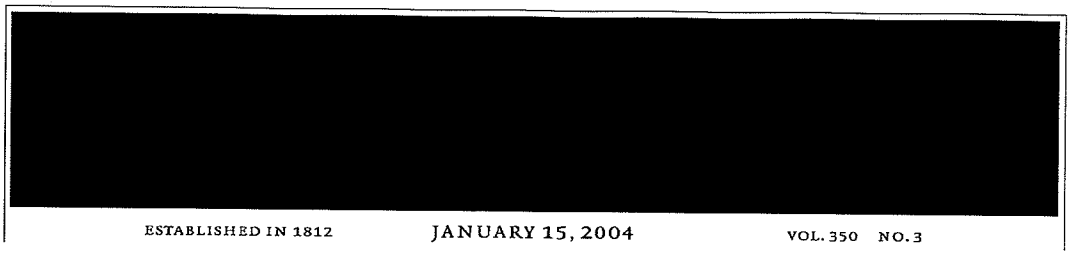

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A Polymer-Based, Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease

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BACKGROUND

Restenosis after coronary stenting necessitates repeated percutaneous or surgical revascularization procedures. The delivery of paclitaxel to the site of vascular injury may reduce the incidence of neointimal hyperplasia and restenosis.

METHODS

At 73 U.S. centers, we enrolled 1314 patients who were receiving a stent in a single, previously untreated coronary-artery stenosis (vessel diameter, 2.5 to 3.75 mm; lesion length, 10 to 28 mm) in a prospective, randomized, double-blind study. A total of 652 patients were randomly assigned to receive a bare-metal stent, and 662 to receive an identical-appearing, slow-release, polymer-based, paclitaxel-eluting stent. Angiographic follow-up was prespecified at nine months in 732 patients.

RESULTS

In terms of base-line characteristics, the two groups were well matched. Diabetes mellitus was present in 24.2 percent of patients; the mean reference-vessel diameter was 2.75 mm, and the mean lesion length was 13.4 mm. A mean of 1.08 stents (length, 21.8 mm) were implanted per patient. The rate of ischemia-driven target-vessel revascularization at nine months was reduced from 12.0 percent with the implantation of a bare-metal stent to 4.7 percent with the implantation of a paclitaxel-eluting stent (relative risk, 0.39; 95 percent confidence interval, 0.26 to 0.59; P<0.001). Target-lesion revascularization was required in 3.0 percent of the group that received a paclitaxel-eluting stent, as compared with 11.3 percent of the group that received a bare-metal stent (relative risk, 0.27; 95 percent confidence interval, 0.16 to 0.43; P<0.001). The rate of angiographic restenosis was reduced from 26.6 percent to 7.9 percent with the paclitaxel-eluting stent (relative risk, 0.30; 95 percent confidence interval, 0.19 to 0.46; P<0.001). The nine-month composite rates of death from cardiac causes or myocardial infarction (4.7 percent and 4.3 percent, respectively) and stent thrombosis (0.6 percent and 0.8 percent, respectively) were similar in the group that received a paclitaxel-eluting stent and the group that received a bare-metal stent.

CONCLUSIONS

As compared with bare-metal stents, the slow-release, polymer-based, paclitaxel-eluting stent is safe and markedly reduces the rates of clinical and angiographic restenosis at nine months.

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THE IMPLANTATION OF CORONARY stents reduces the risk of periprocedural complications and restenosis more than does balloon angioplasty alone.[1,2] Nonetheless, clinical and angiographic restenosis still occurs in a substantial proportion of patients, often necessitating repeated revascularization procedures, decreasing the quality of life, and increasing health care expenditures.[3,4] The principal cause of restenosis after coronary stenting is neointimal hyperplasia resulting from the proliferation and migration of smooth-muscle cells and extracellular matrix production.[5] Numerous systemic pharmacologic and adjunctive device-based approaches have been ineffective at further lowering the risk of restenosis after stenting.[6] Recently, the site-specific delivery of agents capable of interrupting cellular replication has shown promise in inhibiting neointimal hyperplasia.[7] In particular, the polymer-based, sirolimus-eluting stent has proved to be safe and effective in reducing the risk of restenosis in previously untreated lesions of native coronary arteries.[8,9]

Paclitaxel, a lipophilic molecule derived from the Pacific yew tree *Taxus brevifolia*, is capable of inhibiting cellular division, motility, activation, secretory processes, and signal transduction.[10-15] The vascular compatibility and efficacy of paclitaxel in reducing neointimal hyperplasia after balloon- and stent-mediated injury have been shown in in vitro and in vivo studies.[16-21] The potential for a slow-release, polymer-based, paclitaxel-eluting stent to reduce the risk of restenosis after the treatment of short, focal atherosclerotic lesions in humans has been demonstrated in small-to-moderate-sized studies.[22,23] We therefore performed a large-scale, prospective, double-blind, randomized, multicenter trial to examine the safety and efficacy of such a stent in reducing the risk of clinical and angiographic restenosis in a broad population of patients and lesions.

STUDY POPULATION AND PROTOCOL

Patients who were at least 18 years of age, had stable or unstable angina or provokable ischemia, and were undergoing percutaneous coronary intervention for a single, previously untreated lesion in a native coronary artery were considered for enrollment. Clinical exclusion criteria included previous or planned use of intravascular brachytherapy in the target vessel or of any drug-eluting stent; myocardial infarction within 72 hours before enrollment; a left ventricular ejection fraction of less than 25 percent; hemorrhagic diatheses; contraindications or allergy to aspirin, thienopyridines, paclitaxel, or stainless steel; a history of anaphylaxis in response to iodinated contrast medium; use of paclitaxel within 12 months before study entry or current use of colchicine; a serum creatinine level of more than 2.0 mg per deciliter (177 μmol per liter), a leukocyte count of less than 3500 per cubic millimeter, or a platelet count of less than 100,000 per cubic millimeter; a recent positive pregnancy test, breast-feeding, or the possibility of a future pregnancy; coexisting conditions that limited life expectancy to less than 24 months or that could affect a patient's compliance with the protocol; and current participation in other investigational trials. The study was approved by the institutional review board at each participating center, and consecutive, eligible patients provided written informed consent.

Before undergoing catheterization, patients received 325 mg of aspirin and a 300-mg oral dose of clopidogrel, a base-line electrocardiogram was obtained, and creatine kinase and isoenzyme levels were measured. Angiographic eligibility for inclusion was then assessed: patients had to have a single target lesion with a reference-vessel diameter on visual examination of 2.5 to 3.75 mm and a lesion length of 10 to 28 mm that could be covered by a single study stent. Angiographic exclusion criteria included a left main or ostial target lesion, moderate or severe calcification of the target vessel or lesion, tortuosity or angulation, bifurcation of the target lesion (defined by a side branch measuring more than 2.0 mm in diameter with more than 50 percent stenosis), an occluded target lesion (Thrombolysis in Myocardial Infarction grade 0 or 1 flow), or thrombus. Patients were also excluded if the use of atherectomy or cutting balloon was planned before stenting. Enrollment was permitted after the successful treatment of one additional nonstudy lesion in a nonstudy vessel before randomization.

RANDOMIZATION AND STENT IMPLANTATION

Randomization was performed by telephone and was stratified according to the presence or absence of medically treated diabetes mellitus and vessel size (less than 3.0 mm vs. 3.0 mm or more). Patients were assigned in equal proportions in a double-blind fashion with the use of random serial numbers to treatment with either the slow-release, polymer-based, paclitaxel-eluting stent (TAXUS, Boston Scientific) or a visually indistinguishable bare-metal

stent (EXPRESS, Boston Scientific). Unfractionated heparin was administered according to standard practice, and the use of glycoprotein IIb/IIIa inhibitors was at the operator's discretion. After mandatory dilation with the use of a balloon:artery ratio of 1:1, an appropriate-sized stent (approximately 2 to 4 mm longer than the lesion, with a ratio of stent diameter to distal reference-vessel diameter of 1 to 1.1:1) was implanted at a pressure of at least 12 atm. Stents were available in lengths of 16, 24, and 32 mm and in diameters of 2.5, 3.0, and 3.5 mm. Additional study stents could be implanted in the event of edge dissections of types B through E or otherwise suboptimal results, and the use of dilation after stent implantation was at the operator's discretion.

A postprocedural electrocardiogram was obtained, and cardiac enzymes were measured every 8 hours for 24 hours. Patients took 325 mg of aspirin daily indefinitely and 75 mg of clopidogrel daily for six months. Clinical follow-up was scheduled at one, four, and nine months and yearly thereafter for five years.

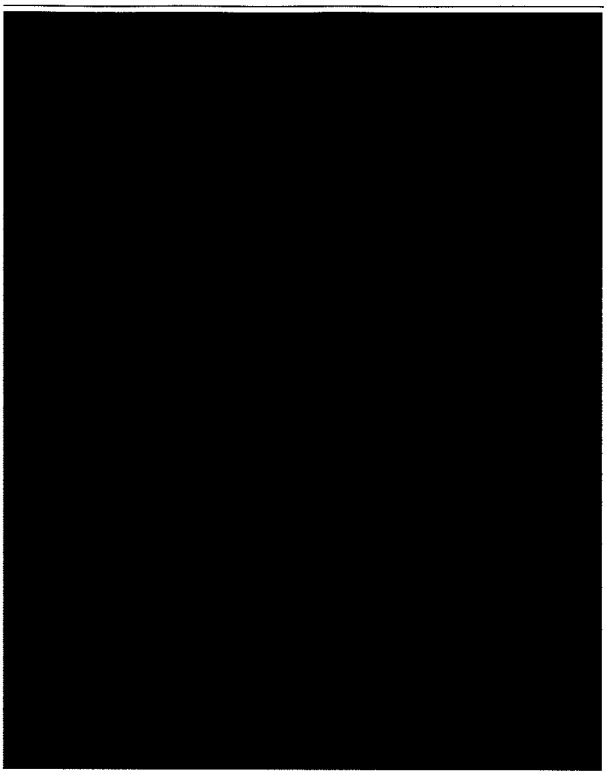
DATA MANAGEMENT

Independent study monitors verified 100 percent of the data on site from case-report forms. Data were maintained in a computerized data base by PAREXEL International, and the investigators had unrestricted access to the data. All major adverse cardiac events were reviewed and adjudicated by an independent committee whose members were unaware of patients' treatment allocation. A data and safety monitoring committee periodically reviewed blinded safety data, each time recommending that the study continue without modification. An independent analysis was performed at the angiographic core laboratory by a technician who was unaware of patients' clinical outcomes, using validated quantitative methods.[24] Measures were reported separately within the stent, within 5 mm proximal and distal to each edge, and over the entire segment that was analyzed (the "analysis segment"). The manuscript was prepared by the principal investigator and revised after the other coauthors reviewed it.

END POINTS AND DEFINITIONS

The primary end point was the nine-month incidence of ischemia-driven target-vessel revascularization, as adjudicated by the independent clinical-events committee. Target-vessel revascularization was considered to be driven by ischemia if the stenosis of the target vessel was at least 50 percent of the luminal diameter on the basis of a quantitative analysis, with either electrocardiographic changes while the patient was at rest or a functional study indicating ischemia in the distribution of the target vessel, or if there was stenosis of at least 70 percent in conjunction with recurrent symptoms alone. Target-lesion revascularization was defined as repeated revascularization for ischemia owing to stenosis of at least 50 percent of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent.

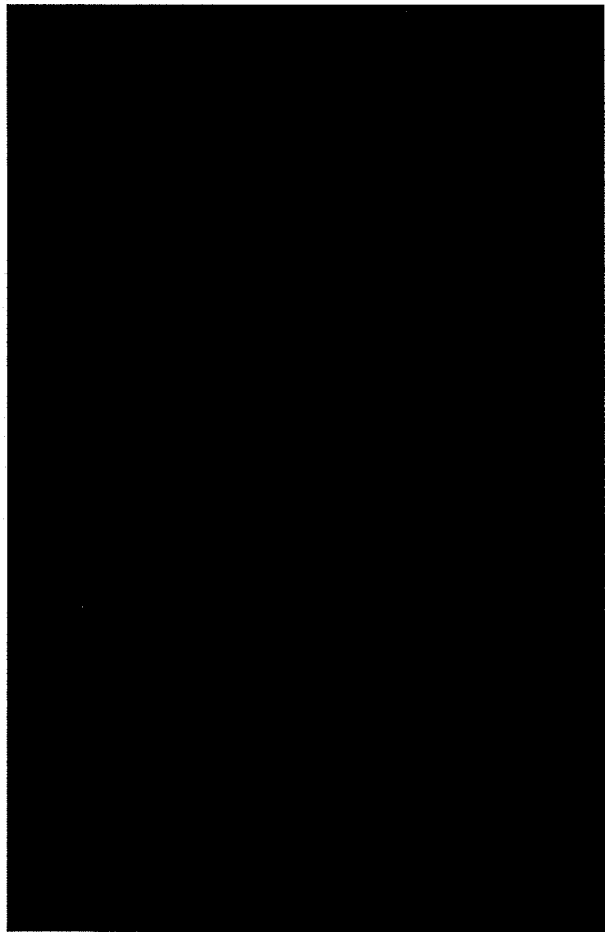
Myocardial infarction after the intervention was defined as either the development of pathologic Q waves lasting at least 0.4 second in at least two contiguous leads with an elevated creatine kinase MB fraction level or, in the absence of pathologic Q waves, an elevation in creatine kinase levels to more than twice the upper limit of normal with an



* Plus–minus values are means ±SD. There were no significant differences between groups.
† Values were visually estimated by the operator; other angiographic measures are quantitative and were made in the core laboratory.

elevated creatine kinase MB level. A creatine kinase level more than five times the upper limit of normal was required to diagnose a myocardial infarction after bypass surgery.

Major adverse cardiac events were defined as death from cardiac causes (if the cause of death was undetermined, it was categorized as cardiac), myocardial infarction, or ischemia-driven target-vessel revascularization. Target-vessel failure was defined as death, myocardial infarction, or ischemia-driven revascularization related to the target vessel. If an adverse event could not conclusively be attributed to a non-target vessel, the event was considered a target-vessel failure.



* Plus–minus values are means ±SD.

Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of either vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel or, in the absence of angiographic confirmation, either acute myocardial infarction in the distribution of the treated vessel or death from cardiac causes within 30 days. Binary restenosis was defined as stenosis of at least 50 percent of the luminal diameter of the treated lesion.

STATISTICAL ANALYSIS

Using a two-sided test for differences in independent binomial proportions with an alpha level of 0.05 and allowing for a 10 percent rate of attrition, we calculated that 1172 patients would have to undergo randomization for the study to have 85 percent power to detect a reduction in the primary end point of ischemia-driven target-vessel revascularization from an anticipated 15 percent after bare-metal stenting to 9 percent with the paclitaxel-eluting stent, a 40 percent relative reduction. The protocol also prespecified that a minimum of 216 patients would be randomly assigned to receive a 32-mm stent, which became available only in the latter part of the study. An additional 154 patients whose lesions were longer than 24 mm therefore underwent randomization, bringing the total number enrolled to 1326 patients.

The principal secondary end point was the extent of stenosis of the target lesion at nine months. The protocol initially prespecified that follow-up angiography be performed in the first 536 consecutive patients enrolled — a number that, assuming a 25 percent rate of attrition, afforded the study 80 percent power to demonstrate a 17 percent reduction in mean (±SD) stenosis, from 27.2 to 22.5±16.7 percent. To make possible adequate angiographic evaluation of long lesions, the angiographic cohort was expanded by 196 consecutive patients who were receiving 24- or 32-mm stents, resulting in a total of 732 patients in the follow-up angiographic cohort.

Categorical variables were compared by means of the likelihood-ratio chi-square test or Fisher's exact test. Continuous variables are presented as means ±SD or medians with interquartile ranges and were compared with the use of Student's t-test or the Wilcoxon two-sample test. The influence of base-line variables on nine-month categorical end points was evaluated with logistic regression with the use of Wald's chi-square test. This analysis included all base-line clinical and angiographic fea-